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The athlete's heart



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Editorial

The death of a fit person, especially when young and apparently healthy, always causes concern. Recent high profile cases have focused attention on screening to identify those who might be at risk, in order to give preventable advice. In addition, cardiac support facilities and experienced personnel need to be available at sporting venues such as soccer grounds and major events such as marathons. However, even the most comprehensive screening cannot and does not exclude sudden death. This raises the question as to whether in the presence of an apparently normal heart sudden intense exercise renders the athlete acidotic to a degree that induces arrhythmias.

In this very timely issue, we address the basics of energy metabolism and how optimizing cardiac energy metabolism can improve cardiac efficiency and function, and move on to clinical scenarios where the focus is on preventing cardiac events. The clinical evaluation of the athlete is comprehensively reviewed by Cox and Sharma and supported by articles demonstrating how to evaluate the athletic heart using imaging techniques. The importance of differentiating physiological from pathological left ventricular hypertrophy and separating healthy normal ventricles from the hypertrophic cardiomyopathic cannot be emphasized enough. It is also important to use pre-participation screening to identify the inherited arrhythmogenic athlete as Corrado et al demonstrate.

Exercise toxicity and the idea that an individual may have a "typical dose-response" in which a level of exercise may be achieved which does more harm than good is thought provoking and Baggish opens the door to the concept that high level exercise is not evidence based with regard to disease prevention.

Given that metabolic changes occur during exercise, which may in certain circumstances be counterproductive, the role of metabolic modification is explored by Chen who links trimetazidine's beneficial effects. Of special concern, as addressed by Ussher et al, is the use of banned performance-enhancing drugs that not only provide unfair advantage but also jeopardize the health of the user.

Pelliccia et [1] review the differences in consensus recommendations between the United States and Europe. I recommend this article and the recent review by Prior and La Gercha [2]

Exercise is an important lifestyle intervention, increasing well being and improving prognosis. While benefit exceeds harm for the vast majority, here we address identifying those vulnerable to exercise induced cardiac problems with prevention our over-riding ambition. •

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Physiological versus pathological left ventricular hypertrophy

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Abstract

Athletes commonly develop what is regarded as a benign increase in cardiac mass in response to physical training. However, prolonged training may lead to a degree of cardiac remodeling that mimics hypertrophic cardiomyopathy (HCM). Left ventricular hypertrophy (LVH) can be defined echocardiographically as a left ventricular wall thickness (LVWT) of greater than 12mm. A LVWT of 12-16mm represents a “grey zone” of overlap between physiological LVH and mild HCM. In this situation, an enlarged left ventricular (LV) cavity size (>56mm) in the absence of symptoms is highly suggestive of physiological LVH. Other markers that favor physiological LVH include normal LV diastolic function, a concentric pattern of hypertrophy, left atrial size <50mm and absence of LV outflow tract obstruction. Where diagnostic doubt remains, Holter monitoring, cardiopulmonary exercise testing, cardiac magnetic resonance imaging or trial of detraining can be considered. The correct diagnosis is essential as HCM increases an athlete’s risk of sudden cardiac death and may result in disqualification from professional sport.

Keywords: left ventricular hypertrophy; hypertrophic cardiomyopathy; athlete’s heart; echocardiography.

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Introduction

Athletes commonly develop what is generally regarded as a benign increase in cardiac mass with associated circulatory and morphological changes in response to physical training. However, prolonged conditioning may eventually result in a degree of cardiac remodeling that mimics certain pathological conditions including hypertrophic cardiomyopathy (HCM).

Echocardiography is fundamental in the assessment of left ventricular hypertrophy (LVH), which is defined as a left ventricular wall thickness (LVWT) greater than 12mm [1,2]. A meta-analysis of almost 1000 echocardiographic studies of highly trained male athletes demonstrated that athletes exhibited a 15–20% increase in septal and left ventricle (LV) posterior wall thickness [3]. A small proportion of athletes may have a LVWT comparable to or overlapping with mild forms of HCM.

The differentiation between HCM and physiological LVH is crucial as HCM accounts for one third of all exercise-related sudden cardiac deaths (SCD) in trained athletes under the age of 35 years [4]. African-Americans account for a disproportionate number of sudden cardiac deaths due to previously undiagnosed HCM [5].

Pathophysiology

Cardiovascular adaptations to training depend upon the form of exercise undertaken. The initial response to isotonic (endurance) training, such as long-distance running and swimming, includes increased maximum oxygen consumption, cardiac output and systolic blood pressure, with an associated decrease in peripheral vascular resistance [6]. Long-term effects include increased maximal oxygen uptake due to increased cardiac output and arteriovenous oxygen difference. The net effect is a volume loaded left ventricle with an increased cardiac output in order to generate a sufficiently large stroke volume.

In contrast, isometric (strength) training, such as wrestling and weight training, causes only mildly increased oxygen consumption and cardiac output in the acute phase, with significant increase in blood pressure, peripheral vascular resistance and heart rate [6]. Long-term, there is no significant increase in oxygen uptake and the net effect is a pressure loaded left ventricle.

Sports such as cycling, rowing and football are examples of combined isotonic and isometric exercise and therefore athletes participating in these sports show a combination of the above responses to varying degrees.

HCM is the commonest genetic heart muscle disease. It is caused by gene mutations encoding proteins within the cardiac sarcomere. Affected individuals exhibit a broad range of phenotypes but typically show a hypertrophied, non-dilated LV in the absence of other causes. LVWT and the extent of LVH may vary from mildly elevated (13–15mm) to massive (>50mm) [7].

At a cellular level, HCM is associated with myocyte disarray, myocardial fibrosis and extravascular collagen deposits. The ventricle is stiff with impaired myocardial relaxation due to abnormal sarcoplasmic calcium kinetics [3]. This results in impaired LV filling and echocardiographic evidence of diastolic dysfunction.

The prevalence of HCM in the general population is 0.2% [8]. The estimated prevalence in athletes is 0.07% based on the Italian pre-participation screening program involving over 34,000 athletes [9]. At least 10% of adolescent patients with HCM may be at unacceptably high risk of sudden cardiac death [10].

The assessment of patients with LVH

History and examination

Patients with HCM may report a family history of sudden cardiac death, an important marker of increased risk in this patient group. Persons with athletic hypertrophy are much less likely to give such a history. There are no specific physical findings distinguishing an athlete with pathological from non-pathological hypertrophy.

12-lead ECG

Approximately 40% of trained athletes have an abnormal resting ECG [6]. The most commonly reported alterations are early repolarization patterns, increased QRS voltages, diffuse T-wave inversion, and deep Q waves. T-wave inversion beyond lead V2 raises the possibility of pathological LVH although there is evidence to suggest that T-wave inversion in V1–V4 should be considered a normal variant in African-American athletes [10].

ECG changes that may suggest HCM rather than physiological LVH include left bundle branch block (LBBB) and ST depression or deep T wave inversion (>0.2mV) in two contiguous leads [7].

Echocardiography

Many large studies have been performed assessing the echocardiographic features of the hearts of trained athletes.

It has been shown that athletes have a significantly greater maximal LVWT, end-diastolic cavity size and LV mass compared to non-athletic controls [11]. Of 720 adolescent athletes, 5% had LVWT greater than upper limit of normal (normal 9–12mm depending upon age and gender). All of these athletes had concentric LVH with greater than predicted LV end-diastolic cavity size and normal mitral inflow velocity patterns [11].

Ethnicity and gender may have an impact on LVWT measurements in athletes. A study of 300 black male athletes and 300 white male athletes showed a prevalence of LVH (LVWT >12mm) of 18% in black athletes compared to 4% in white athletes [3]. Athletes with LVH tend to be males aged over 16 years. A study of over 1000 female Italian athletes had a largest recorded LVWT of 12mm [12].

There exists a so-called “grey-zone” of overlap between physiological LVH and mild HCM in terms of LVWT. This “grey zone” of 12–16mm is present in 2%

of highly trained athletes [7,13] and clearly presents a diagnostic dilemma. In this situation, LV cavity size is the single most important discriminator between physiological LVH and HCM with an enlarged cavity size in the absence of symptoms being highly suggestive of physiological LVH [3]. LV dilatation is recognized in HCM but this is usually a manifestation of end-stage disease associated with New York Heart Association functional class III or IV [14]. Where the LV cavity size is not enlarged, a number of features can be used to differentiate HCM from physiological LVH (Table 1).

HCM is associated with diastolic dysfunction. Echocardiographically, this may manifest as reversed E:A ratio, prolonged E deceleration time (>240ms), low early diastolic velocities ($E' < 9\text{cm/s}$) or reversed S/D ratio on pulmonary vein Doppler. Additionally, $E/E' > 12$ is a hallmark of HCM, and is indicative of raised left atrial filling pressures. Most trained athletes have a $E/E' < 8$ [3]. Left atrial size is often mildly increased in athletes, with up to 50mm in men and 45mm in women rarely being associated with pathological conditions [15]. A left atrial size greater than 50mm in adult athletes raises the possibility of pathological LVH.

Physiological LVH produces a concentric pattern of hypertrophy with a septum to posterior wall ratio of

less than 1.5:1 [15] (Fig. 1). Asymmetrical septal hypertrophy, defined as a septum to posterior wall ratio of 2:1 or greater, is diagnostic of HCM (Fig. 2). LV outflow tract obstruction caused by systolic anterior motion of

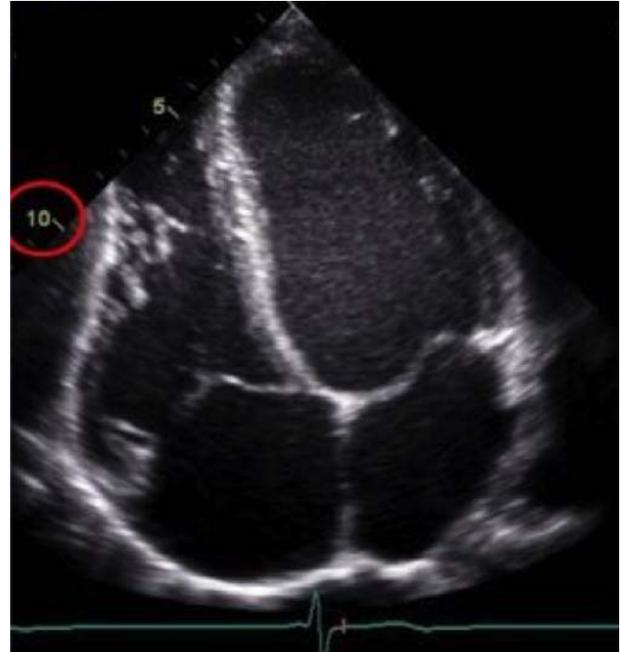


Fig. 1 Athletes heart with dilated LV cavity and overall increased LV mass.

	Features suggestive of athlete's heart	Features suggestive HCM
History	No family history of HCM/SCD	Positive family history HCM/SCD
ECG	ST changes and T wave inversion isolated to V1 and V2	ST depression or T wave inversion in 2 contiguous leads (except V1 and V2), LBBB
Echo LV wall thickness	<12mm	>16mm
Echo LV cavity	>56mm	<56mm
Echo diastolic function	$E/E' < 8$ $E' > 9\text{cm/s}$ Normal E:A ratio E deceleration time < 240ms	$E/E' > 12$ $E' < 9\text{cm/s}$ Reversed E:A ratio E deceleration time > 240ms
Echo LA size	<50mm	>50mm
Echo LVOT velocity	Normal	Obstruction due to systolic anterior motion of AMVL
CPEX	Peak $O_2 > 50\text{ml/kg/min}$	Peak $O_2 < 50\text{ml/kg/min}$
Holter	No NSVT	NSVT
CMR	No post-gadolinium enhancement, Uniform hypertrophy	Post-gadolinium enhancement, Asymmetrical hypertrophy
Impact of deconditioning	2-5mm reduction in LVWT	No change

Table 1 Features that help distinguish a normal athletes heart from a cardiomyopathy. HCM hypertrophic cardiomyopathy, SCD sudden cardiac deaths, LBBB left bundle branch block, AMVL anterior mitral valve leaflet, NSVT non-sustained ventricular tachycardia, LVWT left ventricular wall thickness.

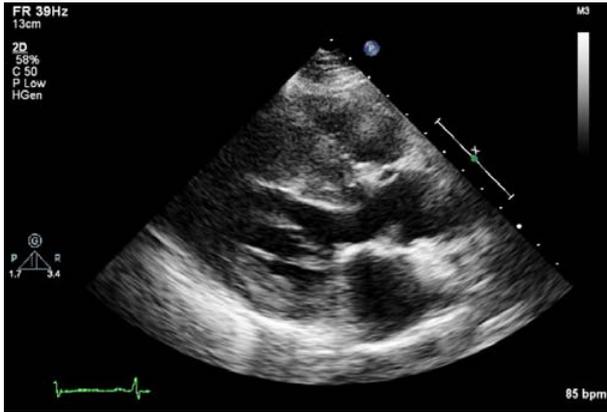


Fig. 2 Hypertrophic cardiomyopathy (HCM) with asymmetrical hypertrophy and reduced LV cavity size.

the anterior mitral valve leaflet (AMVL) is also suggestive of HCM [13].

Further tests may be considered in situations where the diagnosis remains unclear following clinical assessment, ECG and echocardiography (Fig. 3).

Holter monitoring

Holter may be useful to identify episodes of non-sustained ventricular tachycardia (NSVT) that may suggest a pathological cause for LVH.

Cardiopulmonary exercise testing (CPEX)

Most individuals with HCM have low peak oxygen consumption irrespective of symptom status [16]. This is in contrast to high peak oxygen consumption in those with physiological LVH. A peak oxygen consumption > 50 ml/kg/min favors physiological adaption [3]. Exer-



Fig. 3 Equivocal case of 23-year old with symmetrical left ventricular hypertrophy (LVH) and no family history of hypertrophic cardiomyopathy (HCM). However, LV cavity size is normal and there is also evidence of LV diastolic dysfunction.

cise testing is also useful in identifying abnormalities in exercise blood pressure response and exercise induced arrhythmias.

Cardiac magnetic resonance imaging (MRI)

Cardiac MRI can be a useful adjunct to echocardiography in some cases. The superior image quality can identify segmental LV hypertrophy diagnostic of HCM. This may be present in the anterolateral free wall, posterior ventricular septum or the apex. In addition, the demonstration of delayed post-gadolinium enhancement is indicative of replacement fibrosis [17].

Physical deconditioning

Where the diagnosis remains unclear despite other tests, 3 months deconditioning with serial echocardiography or cardiac MRI may be useful. In physiological LVH, deconditioning would be expected to result in a reduction in wall thickness of 2–5mm. Whilst this option may confirm a diagnosis, it can have a quite significant impact on the athlete in terms of physical conditioning and inability to compete for this period, as well as psychological consequences. Understandably, many athletes are reluctant to pursue this option, and discussions regarding this should be handled sensitively.

Impact of diagnosis

The differentiation of physiological LVH from HCM is essential, as athletes with unequivocal or probable HCM should abstain from competitive sport and vigorous training. The identification of cardiovascular disease associated with sudden cardiac death may be basis for disqualification from a sport in order to minimize risk [18]. Additionally, inaccurate diagnosis of HCM may result in unnecessary withdrawal from sport, potentially resulting in both psychological distress and economic losses to the individual [7].

Many professional sporting bodies have adopted screening programs in an effort to identify those at risk of sudden cardiac death. These programs include 12-lead ECG and echocardiogram as a minimum, often with other additional tests. Some countries, such as Italy, have mandatory nationwide programs for professional athletes.

Summary

LVH is usually a normal physiological consequence of regular athletic training. However, a small proportion of

athletes demonstrate LVH which is in fact due to the presence of HCM, and which may put them at unacceptable risk of sudden cardiac death during competitive sport. The current mainstay of investigation is 12-lead ECG and echocardiography, with the use of additional tests where diagnostic doubt remains. Clearly, correct diagnosis is essential as the stakes are high and diagnosis of HCM usually results in disqualification from professional sport. A thorough and accurate assessment is essential to minimize the risk of serious cardiac events in this population group. Appropriate and effective imaging enables the differentiation of benign from pathological causes of LVH in the majority of cases. •

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Clinical evaluation of the athlete

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Abstract

There is a growing body of evidence suggesting that athletic training increases the likelihood of arrhythmias in predisposed athletes, sometimes resulting in sudden cardiac death (SCD). The clinical evaluation of athletes involves a directed history and examination and diagnostic tests including a 12 lead electrocardiogram and other heart rhythm assessment, functional assessment and advanced imaging modalities including echocardiography, cardiac magnetic resonance and computed tomography. This article discusses the diagnostic challenge that sets athletes apart from sedentary individuals: namely the physiological adaptations, referred to collectively as the "athletic heart" that occur as a result of training and that can mimic cardiac pathology.

Keywords: arrhythmias; athlete's heart; clinical evaluation; physiological adaptations; sudden cardiac death.

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Introduction

Since the classical era, athletes have often been considered as some of the greatest heroes of their age. This high regard has continued into modern Western society with athletes being perceived as the supreme combination of health, training, determination and genetic good fortune. It is therefore shocking when an athlete develops cardiac disease or dies suddenly. There is evidence that athletic training can provoke arrhythmias in predisposed individuals, occasionally resulting in sudden cardiac death (SCD). These deaths are the leading cause of non-traumatic death during exercise. The majority of victims of SCD harbour asymptomatic cardiac diseases (Table 1) including inherited cardiomyopathies, channelopathies and structural heart disease, though a significant proportion die from acquired causes such as myocarditis or premature coronary artery disease. In older athletes atherosclerotic coronary artery disease is the most common cause of death.

There are discrepancies relating to the incidence of SCD in younger athletes with estimates ranging between 1 per 23,000 and 1 per 300,000 person years [1]. Regardless of the study however, this number is not insignificant and presents an important problem. Of the deaths in younger athletes, 90% are related to physical exertion, 90% occur in males and black athletes are 2.6 times more susceptible compared with Caucasians. The athlete's sport is also important; the highest incidence of SCD is observed in sports with regular bursts of explosive activity such as American football, soccer, rugby and basketball. In addition to life threatening conditions there is also evidence showing that chronic athletic training increases the risk of atrial fibrillation [2], atrial flutter [3] and sinus node dysfunction [4] in older athletes.

CONGENITAL/INHERITED CAUSES	
Myocardial disease	Hypertrophic cardiomyopathy Arrhythmogenic ventricular cardiomyopathy Dilated cardiomyopathy
Coronary artery disease / anomalies	Anomalous origin of the coronary arteries Premature atheromatous coronary artery disease (age <35 years)
Cardiac conductive tissue abnormalities	Wolff-Parkinson-White syndrome Idiopathic ventricular tachycardia Long-QT syndrome Brugada syndrome Catecholaminergic polymorphic ventricular tachycardia Short-QT syndrome
Valvular heart disease and disorders of the aorta	Mitral valve prolapse Bicuspid aortic valve Marfan's Syndrome
ACQUIRED HEART DISEASE	
Infections	Myocarditis
Drugs	Cocaine, amphetamines, overdoses
Infiltrative disease	Sarcoid, amyloid
Electrolyte disorders	
Hypothermia / hyperthermia	
Trauma (commotio cordis)	
Table 1 Summary of potentially fatal cardiac conditions seen in athletes.	

The diagnostic challenge is that physiological adaptations associated with athletic training, collectively referred to as the “athlete’s heart,” can mimic morphologically mild expressions of disorders implicated in SCD. The differentiation between physiological adaptation and pathology is critical since an erroneous diagnosis has the potential for serious and potentially life changing implications.

The “athlete’s heart”

Exercise training is associated with a number of physiological changes in the cardiovascular system [5,6]. Endurance exercise, such as running, involves a sustained elevation in cardiac output, with a normal or reduced peripheral vascular resistance, resulting in an increased blood volume flowing through all four cardiac chambers. Strength training, such as bodybuilding, involves activity with little increase in cardiac output but significant increases in peripheral vascular resistance, systolic blood pressure and left ventricular afterload. The nature of cardiac adaptation is dependent on the predominant mode of training [7], with the majority of sports combining elements of both endurance and strength training.

Endurance athletes may increase their cardiac output from a resting level of 5–6 liters/min to 40 liters/min at peak exercise. The rise in cardiac output is achieved by an increase in heart rate and augmentation of the stroke volume. Although resting systolic function in athletes is no different to sedentary controls [8], there is evidence of augmentation of early diastolic filling [9]. The majority of the increased stroke volume therefore arises primarily from increased chamber dimensions. Exercise produces an increased haemodynamic load on the aorta which results in remodeling with aortic dilatation [10].

Clinical evaluation

Athletes may present in one of three ways: as part of a pre-participation medical screening, as part of a medical consultation for another reason, for evaluation of symptoms suggestive of cardiac disease. The approach to all three is similar and requires the eliciting of a relevant clinical history and cardiovascular examination. Depending on their outcome further investigations may be indicated.

History and physical examination

Both screening and symptom-directed evaluation of the athletic patient should concentrate on identifying

the occurrence of a number of relevant cardiogenic symptoms including exertional chest pain or discomfort, breathlessness disproportionate to the amount of exercise being performed, palpitations and syncope. These symptoms occur in 35% of young patients prior to SCD [11]. In the event of syncope an eyewitness account of the episode can be helpful. Differentiating syncope from epilepsy is clinically difficult. In general all athletes with a label of epilepsy should be investigated for an arrhythmogenic cardiac disorder. A thorough family history is crucial given the inherited nature of most conditions implicated in SCD. A family history of known hereditary cardiac disease, sudden or premature cardiac death in relatives under the age of 50 years warrants comprehensive cardiac evaluation. Furthermore, a family history of epilepsy, syncope, unexplained drowning or road traffic accidents may be vital clues to a potentially fatal hereditary disorder. It is important to identify the use of medications associated with prolongation of the QT-interval and recreational or performance enhancing drugs such as cocaine, amphetamines and anabolic steroids which may be implicated in cardiomyopathy and arrhythmogenesis.

The physical examination should focus on the identification of peripheral stigmata of hypercholesterolaemia, hypertension, co-arctation of the aorta, valvular heart disease and Marfan's syndrome although most causes of SCD are associated with normal physical examination.

Pre-participation screening with an ECG

Pre-participation screening is a highly contended area with differences in opinion as to whether athletes should undergo a routine ECG screening. Using evidence of reduced mortality in athletes resulting from the program of Italian national pre-participation screening [12], the current European Society of Cardiology (ESC) guidelines [13] recommend routine acquisition of a resting 12 lead ECG. The American Heart Association take an opposing stance [14] due to the large financial and logistical requirements of implementation of such a program at National level [15]. Whether an ECG is routinely performed in the absence of relevant history or examination findings is beyond the scope of this article; however an abnormal ECG may be the only clinical manifestation of a quiescent cardiac disorder.

The 12-lead ECG

Whenever there is a clinical indication, a 12 lead ECG should be routinely performed. The athletic adaptation in autonomic activation is at least partially responsible for the common ECG findings of sinus bradycardia, first degree and Mobitz type I second degree atrioventricular nodal block, an increase in premature beats and altered repolarisation (seen as J-point elevation, ST-segment elevation and high amplitude T-waves). Up to two thirds of athletes demonstrate ECG criteria for left ventricular hypertrophy (LVH) [16,17]. Race is an important factor in repolarisation abnormalities in particular as they occur twice as often in black athletes when compared to Caucasian athletes [18]. However, there is considerable overlap between repolarization changes observed in athletes with those identified in disorders implicated in SCD. Therefore ECG changes must always be interpreted within the individual's context. The ESC have produced guidelines [19] where ECG changes are divided into Group 1 and Group 2 (Table 2). The former are considered common, training-related ECG changes that in isolation are not an indication for further investigation, while the latter are uncommon and should trigger further investigation.

The ECG is limited in that it fails to diagnose most cases of coronary artery stenoses and potentially serious coronary artery anomalies. The main concern with ECG screening is the potentially high number of false positive findings as a result of athletic heart adaptations. Using the ESC guidelines on ECG interpretation however this proportion can be significantly reduced to less than 10% [20,21]. A normal ECG however, has a very strong negative predictive value in excluding cardiomyopathies [22]. It is also useful in identifying accessory pathways and ion-channelopathies such as congenital long QT syndrome and Brugada syndrome.

Heart rhythm assessment

Detailed guidance on investigating arrhythmias has been published [23] and the following is a brief overview only. In athletes presenting with symptoms it is often useful to perform prolonged cardiac monitoring with a Holter monitor. While sinus bradycardia, first degree heart block and second degree heart block (Wenkeback type) are usually normal, second degree atrioventricular (AV) block (Mobitz Type II) or third degree AV block should be considered pathological if

Group 1: Common and training-related ECG changes	Group 2: Uncommon and training unrelated ECG changes
<ul style="list-style-type: none"> • Sinus bradycardia • First-degree AV block • Incomplete RBBB • Early repolarisation • Isolated QRS voltage criteria for left ventricular hypertrophy 	<ul style="list-style-type: none"> • T-wave inversion • ST-segment depression • Pathological Q-waves • Left atrial enlargement • Left-axis deviation / left anterior hemiblock • Right-axis deviation / left posterior hemiblock • Ventricular pre-excitation • Complete LBBB or RBBB • Brugada-like early repolarisation
<p>Table 2 Classification of abnormalities of the athlete's electrocardiogram [19]. AV atrioventricular, RBBB right bundle branch block, LBBB left bundle branch block.</p>	

the bradyarrhythmia persists after a 6-week period of detraining or in the presence of symptoms. An exercise stress test is useful for provoking arrhythmias associated with adrenergic surges such as right ventricular outflow tract ventricular tachycardia, polymorphic ventricular tachycardia associated with congenital long QT 1 and 2, and the identification of catecholaminergic polymorphic ventricular tachycardia. In individuals with infrequent palpitations without syncope, a portable Cardiomo device may be required in order to capture the cardiac rhythm during symptoms. In athletes with infrequent syncope an implantable loop recorder may be useful. In selected patients with a history suggestive of recurrent vasovagal syncope, tilt table testing may be indicated.

Functional assessment

Apart from the identification of exercise induced arrhythmias functional testing with cardiopulmonary exercise testing is used to assess fitness in athletes with structurally normal hearts who are experiencing a decline in performance. An exercise test may expose myocardial ischaemia and may be particularly useful in differentiating structural changes associated with physical training from cardiomyopathy.

Imaging assessment

An understanding of the normal limits of adaptive remodeling is critical in differentiating athletic adaptations from cardiomyopathy. In a cohort of 1309 elite male and female athletes [24] 14% had LV dilatation, with left ventricular end-diastolic diameter (LVEDD) >60mm, a dimension compatible with a dilated cardiomyopathy

diagnosis. This increase in cavity size was not observed in strength-trained athletes [6]. Factors that appear to play a role in the development of larger cavity dimensions with LVH include male gender, endurance sports, a longer duration of training, increased body mass and adult physical maturity. While mild aortic root dilatation is common, a diameter of >40mm is rare and associated with increased height, though not necessarily Marfan's syndrome [25].

LVH occurs both as eccentric hypertrophy as a result of the dilated cavity in endurance athletes, but also as a result of concentric hypertrophy in both endurance and strength-trained athletes. Within a cohort of 947 athletes however only 1.7% of male and no females participants developed a wall thickness of ≥ 13 mm—an arbitrary cut-off, but a significant one as it may overlap with hypertrophic cardiomyopathy [26]. In this study all the individuals with wall thickness ≥ 13 mm also had LV cavity dilatation which is not a feature of hypertrophic cardiomyopathy.

Transthoracic echocardiography is a cheap and effective tool to allow the exclusion of many structural abnormalities and it is still the best modality to assess valvular function. Athletes usually have excellent ultrasound windows and in a majority of cases it is even possible to visualize the coronary artery origins. In cases where better visualization of valvular or other structural abnormalities are required transoesophageal echo or other imaging modalities often offer additional benefits. The overlap between the structural findings of the athletic heart and cardiomyopathies mean echo alone is occasionally non-diagnostic and other imaging modalities are required. The role of Computed

Tomography (CT) and cardiac magnetic resonance (CMR) in athletes is reviewed in depth elsewhere [27] and while both are excellent in specific cases, they are required infrequently. CMR with gadolinium contrast is valuable for differentiating between normal myocardium, cardiomyopathies and infiltrative diseases and to localize focal fibrosis or scar. CMR is particularly useful in visualizing the left ventricular apex and right ventricle. It involves no radiation dose but is relatively expensive, time-consuming, can cause claustrophobia and is contraindicated in patients with pacemakers or other metallic foreign bodies or severe renal disease. CT has the advantage of being a quick procedure and if the exclusion of significant coronary artery plaque is required it has a high negative predictive value. The disadvantage of the previously considerable radiation dose has been relatively reduced by recent advances in radiation reduction techniques. Both CMR and CT are appropriate investigations to exclude anomalous coronary arteries.

Differentiating between athletes heart and cardiomyopathy

The overlap of athlete's heart with hypertrophic cardiomyopathy (HCM) is often referred to as the "grey zone" (Fig. 1). Repolarisation abnormalities and a maximum left ventricular wall thickness of $\geq 13\text{mm}$ are unusual but potentially normal findings in athletes. However such findings are common in HCM and so should prompt further investigation. Imaging is usually the key to diagnosis but detraining for 6 weeks may be a useful adjunct as the majority of ECG abnormalities due to athletic activity resolve. Echocardiographic features suggestive of HCM include systolic anterior motion of the anterior mitral valve leaflet, mitral leaflet elongation, LV outflow tract obstruction, impaired diastolic function and a small LV cavity. CMR has emerged as a useful imaging modality to differentiate between causes of LVH [28]. CMR in HCM demonstrates characteristic patchy late gadolinium enhancement (LGE), abnormal LV architecture, several characteristic patterns of hypertrophy, and diffuse perfusion defects. A final method to differentiate athlete's heart from pathological hypertrophy [29], is if the maximum end-diastolic wall to volume ratio $>0.15 \text{ mm/m}^2/\text{ml}$.

There is a similar overlap with the athletes heart and dilated cardiomyopathy (DCM) where again CMR is useful in demonstrating a characteristic mid-wall LGE

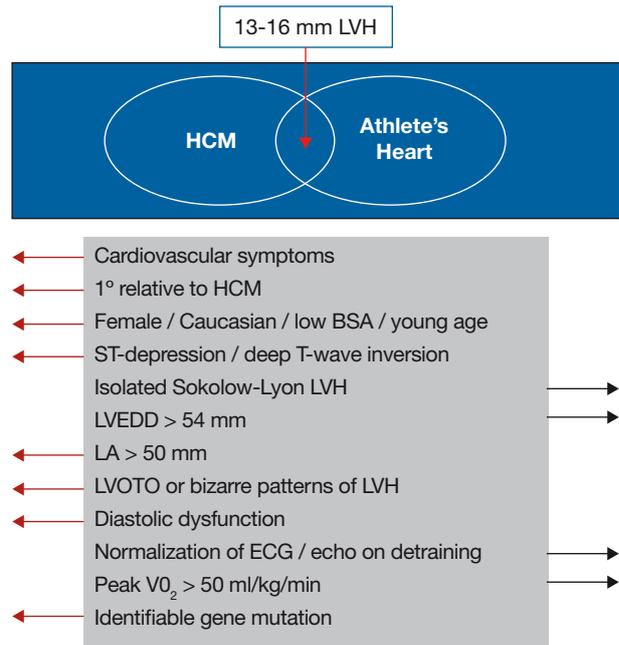


Fig. 1 Clinical criteria used to differentiate athlete's heart from HCM in cases with a borderline degree of LVH of 13–16mm [6]. LVH left ventricular hypertrophy, HCM hypertrophic cardiomyopathy, BSA body surface area, LVWT left ventricular wall thickness, LVEDD left ventricular end-diastolic diameter, LA left atrium, LVOTO left ventricular outflow tract obstruction, VO_2 oxygen consumption.

and when relevant, non-compaction. The differentiation is usually more straightforward however as impaired systolic and diastolic function will also be present in DCM. CMR is the imaging modality of choice in the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) where the findings of right ventricular dilatation, focal aneurysms and regional wall motion abnormalities, and fibrofatty myocardial infiltration of the apices are part of the diagnostic criteria for the disease [30].

Summary

The initial clinical assessment of the athlete follows the same template as any other patient. However, the physiological adaptations developed as a result of chronic athletic training need to be understood to reduce the number of false positive tests and to prevent erroneous diagnoses. The differentiation between adaptive physiology and pathology has improved in the last decade with additional investigational tools becoming widely available including improved non-invasive testing and imaging modalities that make this differentiation easier to make. •

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Athlete's heart or hypertrophic cardiomyopathy

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Abstract

There is overwhelming evidence that the heart of athletes may differ from that of non-athletes, provided that the training is of sufficient intensity and duration (athlete's heart). Predominantly eccentric left ventricular (LV) hypertrophy is observed in sports with high dynamic and low static demands (e.g. running). Sports with high static demands (e.g., weight lifting) lead to predominantly concentric hypertrophy. In sports with high dynamic and high static demands (e.g., cycling) the hypertrophy is compatible with mixed eccentric-concentric hypertrophy. The role of exercise is shown by the study of athletes in different training states. LV systolic function appears to be normal in athletes, both when measured at rest and during exercise. LV diastolic function is on average normal at rest, but is enhanced during exercise, which favors adequate filling of the ventricle at high heart rates. Investigations at the cardiac cellular, molecular and metabolic level confirm that cardiac hypertrophy in response to exercise should be considered physiological. LV wall thickness may be ≥ 13 mm in highly trained male athletes and ≥ 11 mm in female athletes, but the upper physiological limit appears to be 15mm and 13mm, respectively. Key features in the distinction between athlete's heart and hypertrophic cardiomyopathy are the appropriately increased size of the LV internal dimension in endurance athletes, and the normal systolic and particularly diastolic LV function in endurance and strength athletes, apart from history, type of hypertrophy, exercise performance and regression of structural changes with detraining.

Keywords: athlete's heart; hypertrophic cardiomyopathy; echocardiography; endurance training; static training.

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Cardiac enlargement in athletes had already been recognized at the end of the nineteenth century through careful percussion of the chest in cross-country skiers, and was later confirmed by use of radiography and by evidence from autopsy. The advent of echocardiography and magnetic resonance imaging (MRI) allowed investigators to gain a better insight into the heart of athletes and the impact of different sports on cardiac structure and function. However, the heart of athletes may occasionally mimic certain pathological conditions associated with sudden death, such as hypertrophic cardiomyopathy (HCM), so that the distinction between athlete's heart and HCM is of crucial importance, particularly in the grey zone of overlap of structural cardiac changes.

Athlete's heart: structure and function

There is little doubt that repeated exercise stimuli of sufficient duration and intensity may induce cardiac enlargement in response to the exercise-induced hemodynamic changes and altered loading conditions of the heart. Left ventricular (LV) hypertrophy (LVH) has been observed in athletes [1–6], but cardiac adaptations also occur in sedentary subjects in response to physical training [7]. However, there is less unanimity on the relationship between the type of exercise and the specific cardiac adaptations [1–6,8,9]. As early as 1975, Morganroth et al [1] reported that athletes participating in endurance exercise had increased LV mass (LVM) with cardiac changes similar to those in chronic volume overload (eccentric LVH) and that athletes participating in static exercise had increased LVM

similar to those in chronic pressure overload (concentric LVH). These cardiac adjustments serve to counter-balance the increase in wall stress [10]. However, the “Morganroth hypothesis” has been debated because athletic conditioning is rarely purely dynamic or static and the training programs of different athletes may overlap [2–6,8,9]. The results of a first meta-analysis [2] are shown in Table 1, in which the hypothesis of divergent cardiac adaptations in different sports was tested based on echocardiographic studies involving male competitive athletes and non-athletic control subjects, matched for age and body surface area, a strong determinant of cardiac dimensions. As shown in panel A, long-distance runners, a proper example of endurance exercise, have increased LV internal diameter and wall thickness, as expected. However, the

A. LONG-DISTANCE RUNNERS				
	N	controls	runners	P
Age (yr)	9	24.2 ± 1.06	26.9 ± 1.61	NS
HR (b/min)	8	65.7 ± 2.56	51.6 ± 0.80	< 0.001
LVID _d (mm)	10	48.3 ± 0.42	53.2 ± 0.66	< 0.001
IVST _d (mm)	8	9.3 ± 0.36	10.8 ± 0.27	< 0.01
PWT _d (mm)	10	8.9 ± 0.30	10.5 ± 0.29	< 0.001
LVM (g)	10	149 ± 6.2	216 ± 7.3	< 0.001
h/R	10	0.372 ± 0.015	0.398 ± 0.011	= 0.05
B. STRENGTH ATHLETES				
	N	controls	strength athletes	P
Age (yr)	7	24.5 ± 1.49	24.5 ± 1.29	NS
HR (b/min)	7	67.2 ± 2.06	62.3 ± 1.77	NS
LVID _d (mm)	7	51.9 ± 1.07	53.2 ± 0.99	< 0.01
IVST _d (mm)	7	8.9 ± 0.28	10.3 ± 0.48	< 0.05
PWT _d (mm)	7	8.4 ± 0.31	9.5 ± 0.55	< 0.05
LVM (g)	7	159 ± 6.3	198 ± 7.7	< 0.01
h/R	7	0.334 ± 0.016	0.375 ± 0.026	< 0.05
C. CYCLISTS				
	N	controls	cyclists	P
Age (yr)	4	25.2 ± 0.85	23.9 ± 0.89	NS
HR (b/min)	4	67.8 ± 2.4	52.0 ± 0.33	< 0.01
LVID _d (mm)	4	50.5 ± 1.25	55.1 ± 0.6	< 0.05
IVST _d (mm)	4	9.1 ± 0.32	11.7 ± 0.6	< 0.01
PWT _d (mm)	4	8.9 ± 0.48	11.6 ± 0.75	< 0.01
LVM (g)	4	159 ± 4.7	262 ± 22.0	= 0.01
h/R	4	0.357 ± 0.022	0.42 ± 0.021	< 0.05

Values are weighted means ± SE.
 N number of study groups for which the respective variables were reported or could be calculated, HR heart rate, LVID left ventricular internal diameter, IVST interventricular septal thickness, PWT posterior wall thickness, LVM left ventricular mass, h/R relative wall thickness, d at end-diastole.

Table 1 Results of meta-analyses of athletes versus non-athletic controls, matched for age and body size. Data from [2].

meta-analysis also reveals that relative wall thickness, that is the ratio between wall thickness and internal diameter, was 8% higher than in controls, compatible with “predominantly eccentric LVH” rather than pure eccentric LVH. Several sports are categorized as predominantly static or involve power training, such as weight lifting, bodybuilding, wrestling and throwing events. As shown in panel B, relative wall thickness was 12% higher than in controls in these athletes, but there was also a small but significant 2.5% increase in LV internal diameter, compatible with “predominantly concentric LVH.” Finally, cycling and rowing involve both dynamic and static exercise. As shown in panel C, LV internal diameter, wall thickness and LVM were larger in the athletes. In addition, relative wall thickness exceeded that of the control subjects by 19%, indicating that cycling is not only associated with an increase of the internal diameter but also with a substantial disproportionate thickening of the wall, compatible with “mixed eccentric-concentric LVH.” In a subsequent meta-analysis, Pluim et al [3] confirmed the hypothesis of the existence of an endurance-trained and a strength-trained heart, and that divergent cardiac adaptations do occur in athletes performing dynamic and static sports. However, as suggested before [2,4,9], the classification as an endurance-trained heart or a strength-trained heart is not an absolute and dichotomous concept but rather a relative concept. In fact, in every form of endurance training, blood pressure increases (pressure load), in addition to the increase in cardiac output (volume load), just as in every form of strength training, heart rate, cardiac output and blood pressure increase [3]. Cardiac hypertrophy in athletes has in general been confirmed with MRI [5,11,12], but it was suggested that more data are

needed with regard to adaptations to different types of training [5]. It is of note that, despite common use of the term LVH, LVM does not necessarily exceed normal values, so that the term “LV remodeling” may be more appropriate to describe LV adaptations in the athlete.

In addition to the cross-sectional studies, Table 2 summarizes data from studies in which competitive athletes engaged in predominantly dynamic sports were assessed in an active training period and in a period of (relative) rest [2,13]. The significantly larger LVM and its components in the active period shows that physical training per se is at least partly responsible for athlete’s heart. Later on, Pelliccia et al [14] observed that LV cavity dimension, wall thickness and mass had significantly decreased after an on average 5.6-year deconditioning period. However, normalization of structural cardiac changes may not always be complete, even after many years of deconditioning. Whereas athlete’s heart is at least partly due to the training per se, twin studies revealed significant heritability of LV wall thickness, so that cardiac alterations in athletes may be partly genetic [15].

With regard to the right ventricle (RV), Scharhag et al [12] showed by use of MRI that the ratio of the LV to RV end-diastolic volume was similar in endurance athletes and matched controls and concluded that regular and intensive endurance training results in a balanced enlarged heart. Similarly, atrial enlargement is proportional to the enlargement of the ventricles [6].

The meta-analysis on long-distance runners, cyclists and strength athletes, and the results from other sports, revealed that a number of indices of systolic function were usually not different between athletes at rest and matched control subjects [2,3,9]. In cyclists the

	N	Inactive	Active-Inactive	P
HR (beats/min)	11	56.8 ± 1.55	-3.3 ± 1.23	< 0.05
LVIDd (mm)	11	53.6 ± 1.01	+1.1 ± 0.45	< 0.05
IVSTd (mm)	9	10.5 ± 0.26	+0.7 ± 0.23	< 0.05
PWTd (mm)	11	10.2 ± 0.32	+0.5 ± 0.23	< 0.05
LVM (g)	11	214 ± 12.6	+25.7 ± 6.4	< 0.01
h/R	11	0.384 ± 0.0064	+0.017 ± 0.0078	= 0.05
VO ₂ peak (mL/min/kg)	6	60.9 ± 2.89	+4.8 ± 0.49	< 0.001

HR heart rate, LVID left ventricular internal diameter, IVST interventricular septal thickness, PWT posterior wall thickness, LVM left ventricular mass, h/R relative wall thickness, d at end-diastole, VO₂ oxygen uptake

Table 2 Results of the meta-analysis of longitudinal observations in 11 groups of athletes: data from the inactive period and change from the inactive to the active period. Data from [2].

relationship between LV fractional shortening index and systolic wall stress was similar to that obtained in matched sedentary subjects [16]. In addition, the increase of fractional shortening or ejection fraction on dynamic exercise was not different from controls in endurance athletes [17]. Finally, systolic LV function remained unaltered in the longitudinal studies, in which athletes were assessed in different training states [2] and long-term deconditioning did not alter LV ejection fraction [14]. The data therefore suggest a normal LV systolic function in athletes. The overall evidence obtained with different techniques suggests that LV diastolic function at rest is similar in athletes and non-athletes [3,9,16]. However, there is evidence that LV diastolic function is enhanced in the exercising endurance-trained athlete as compared with untrained control subjects [9,17], which favors adequate filling of the ventricle when the diastolic period gets shorter at higher heart rates. Brisk filling of the athlete's ventricle may at least in part be due to the larger chamber [6].

In addition to the results from imaging studies, cardiac hypertrophy in response to exercise training is also considered physiological hypertrophy at the cellular and molecular level [18–20]. Cardiac hypertrophy is characterized by normal organization of cardiac structure and preserved or even enhanced cardiac function, whereas pathological hypertrophy associated with pressure or volume overload, such as in hypertension or valve disease, is commonly associated with up-regulation of fetal genes, fibrosis and cardiac dysfunction. Physiological and pathological hypertrophy are mediated by distinct signaling molecules. Cellular adaptations to exercise with training are due to the activation of signaling pathways, and in particular the IGF-1/IGF-1R/Akt axis appears to have a major role. In addition, Ellison et al [20] reviewed the evidence that the endurance training-induced cardiomyocyte hypertrophy is accompanied by appropriate neo-angiogenesis and that recent data suggest that physical exercise determines cardiac growth also through new cardiomyocyte formation. With regard to cardiac metabolism, myocardial fatty acid utilization [21] and myocardial high-energy phosphate metabolism [22,23] appeared to be similar in endurance-trained athletes and sedentary subjects.

Athlete's heart versus hypertrophic cardiomyopathy

Pelliccia et al [24] reported on 947 amateur competitive athletes during period of intense training and con-

cluded that a LV wall thickness of ≥ 13 mm is only present in about 2%, and that it is associated with an enlarged LV cavity and normal systolic and diastolic function. In addition, the upper limit to which the thickness of the LV ventricular wall may be increased by athletic training appears to be 15mm. However, LV wall thickness was between 13 and 16mm in about one third of competitive road cyclists, but it is of interest that systolic and diastolic function was normal and not different between those with and those without wall thickness of ≥ 13 mm [9]. Lower upper limits of normal have been described in female [25] and adolescent junior athletes [26].

It is likely that male and female athletes with wall thickness of more than, respectively, 15mm and 13mm, and with non-dilated LV cavity, have primary forms of pathologic hypertrophy, such as HCM. However, wall thickness may be in the grey zone, that is 13–15mm in male athletes and 11–13mm in female athletes, which may overlap with patients with a mild HCM phenotype. Table 3 summarizes a number of characteristics of, respectively, HCM and athlete's heart, which may help to distinguish between the two conditions, including family history, electrocardiographic changes, characteristics of the hypertrophy, regression of structural changes with detraining, LV function and exercise performance [27,28]. Key features in the distinction between physiological LVH and HCM are the appropriately increased size of the LV internal dimension in endurance athletes, and the normal systolic and particularly diastolic LV function in endurance and strength athletes. It has been suggested, based on the comparison of group averages, that Doppler echocardiographic assessments of diastolic function may contribute to distinguish physiological from pathophysiological hypertrophy, but their value for the individual subject is limited [25,29]. Also tissue Doppler imaging may help in distinguishing athlete's heart from HCM [30]. Similarly, the myocardial velocity gradient measured across the LV posterior wall may contribute to discriminate between HCM and hypertrophy in athletes [31]. Finally, contrast-enhanced cardiovascular magnetic resonance with late gadolinium enhancement can detect areas of myocardial fibrosis, which are present in most patients with HCM but not in physiological hypertrophy [27]. Because ECG abnormalities such as abnormal QRS-pattern and repolarization changes are part of athlete's

Characteristics of hypertrophic cardiomyopathy.

- Family history positive for hypertrophic cardiomyopathy, syncope and/or sudden death
- Bizarre ECG changes, though abnormal pattern of the QRS-complex and repolarization abnormalities may also be part of athlete's heart
- Asymmetric left ventricular hypertrophy, favoring the interventricular septum
- Normal or reduced left ventricular end-diastolic diameter (<45mm)
- Abnormal left ventricular diastolic function
- Left ventricular outflow tract obstruction during stress echocardiography
- Peak oxygen uptake less than predicted by age, gender and body size
- CMR-gadolinium delayed enhancement
- Positive genetic testing

Characteristics of athlete's heart (endurance training)

- Prolonged conduction delays on ECG (sinus bradycardia; atrioventricular block)
- Enlarged left ventricular end-diastolic diameter (>55mm), with proportional and symmetric increase in wall thickness (eccentric left ventricular hypertrophy)
- Harmonious increase in right ventricular dimension
- Regression of structural cardiac changes with detraining
- Normal left ventricular diastolic function
- Peak oxygen uptake greater than predicted by age, gender and body size

Table 3 Criteria for distinguishing between athlete's heart and mild non-obstructive hypertrophic cardiomyopathy when left ventricular wall thickness falls within the grey zone (13-15mm in males and 11-13mm in females). ECG electrocardiogram, CME cardiac magnetic resonance.

heart [4], the ECG is not appropriate to distinguish definitively between athlete's heart and HCM, but deep Q-waves and negative T-waves are not typical for physiological hypertrophy and are therefore suspicious of HCM [28].

Conclusion

The distinction between physiological cardiac hypertrophy and HCM is important because HCM is the most common cause of sudden death in young athletes and leads to disqualification from intense competitive sports. A pre-participation screening program, including a 12-lead ECG, has been developed by the European Society of Cardiology [32], based on the 25-year experience in Italy, where the systematic pre-participation screening of competitive athletes may have led to a reduced incidence of sudden cardiovascular death [33]. •

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To train or not train? That is the question

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Abstract

The health benefits of routine physical exercise are numerous and incontrovertible. But, is it as good as it seems? We are continuing to accumulate evidence that long-term exposure to intense exercise may increase the incidence of certain cardiovascular conditions. We should simultaneously be aware that exercise, like all physiologic stimuli, probably behaves in a typical dose-response fashion in which an individual can reach levels that do more harm than good. Recognizing the patient who exercises excessively may be challenging and requires careful attention to subjective symptomatic reports and temporal exercise patterns. In clinical cardiovascular practice, lessons learned from the science of human performance including the need for dedicated rest and training periodicity may prove applicable to our patients and may be the best defense against the toxicity of excessive exercise.

Keywords: athlete's heart; cardiomyopathy; exercise physiology; overuse injury.

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The health benefits of routine physical exercise are numerous and incontrovertible. Virtually all common cardiovascular disease processes including atherosclerosis [1], dyslipidemia [2], and hypertension [3], respond favorably to routine aerobic exercise. As such, essentially every professional medical organization involved in clinical practice oversight encourages physicians to prescribe exercise for primary prevention, risk factor modification, and treatment of established disease. Guidelines delineating exercise recommendations are widely available and exercise prescription should be considered a mandatory component of health maintenance and disease treatment for all patients [4,5].

While the cardiovascular medical community has spent a good deal of time developing strategies to motivate the sedentary, there is a fascinating phenomenon evolving at the other end of the exercise spectrum. A rapidly growing segment of the general population is engaging in high levels of physical exercise that far exceed the volume and intensity that have been associated with disease prevention. Intense, high volume exercise training, historically the purview of young, naturally endowed, elite competitors, is now being practiced by men and women of all ages. Evidence of this trend can be found in numerous places with none more compelling than participation rates among recreational sporting events like running road races. Records from the United States indicate a veritable explosion in the number of individuals participating in this activity [6]. There are several explanations for this increase in popularity including mounting awareness of the health benefits of exercise, simple enjoyment of sport, pleasure derived from the sense of belonging to sporting communities, and fulfillment of competitive and

achievement-based drives. This exciting phenomenon is refreshing and seems poised to offset the record levels of obesity and cardiovascular disease that are crippling the human race. But, is it as good as it seems?

The growth of high-level recreational exercise has been accompanied by emerging data suggesting that exercise may lead to overuse cardiovascular pathology [7,8]. This should not come as a surprise. Exercise, like any physiologic stimulus, is not a binary phenomenon and must be considered as a continuous variable. Quantification of exercise, though somewhat challenging in clinical and research settings, is of paramount importance in the context of any discussion about its risks and benefits. The two basic parameters that define the exercise exposure or “dose,” much like the strength and frequency with which we prescribe medications, are intensity and volume. These concepts are familiar to those who work in the cardiac rehabilitation setting but are infrequently used in the clinical assessment of athletic patients. Like all physiologic and biological stimuli, exercise follows a dose-response curve coupling increasing effects with increasing exposure to a point of toxicity at which further increase may do more harm than good. In routine clinical practice, we strive often fruitlessly to motivate our patients to exercise enough to exceed the threshold level at which the benefits of exercise begin to accrue. In contrast, the avid athlete may push exercise to upper end of the curve at which point negative results (i.e., toxicities) begin to develop.

The concept of exercise toxicity, most commonly referred to as overuse injuries or overuse syndromes, is well recognized. Examples include skeletal stress fractures, chronic tendonopathies, and acquired amenorrhea. The notion that the concept of overuse injury can apply the cardiovascular system is only now beginning to crystallize. Reports documenting cardiac fatigue with biochemical evidence of mild cardiac damage following prolonged exercise continue to accumulate [9–11]. While this concept remains incompletely understood, the bulk of available evidence suggests that the myocardium behaves like skeletal muscle in that it can fatigue if worked hard over an extended period of time. Reductions in contractility (systolic function) and lusitropy (diastolic function) of both the right and left ventricle have been documented following completion of marathon runs, long distance

cycling events, and triathlons [12,13,11]. Studies with extended follow-up demonstrate normalization of function within hours to days of event completion suggesting that the vast majority of the observed functional deterioration is transient and fully reversible. But, the impact of repetitive bouts of exercise sufficient to induce cardiac fatigue remains uncertain.

Cardiac adaptations to exercise are well documented and have a focus of scientific inquiry for more than 100 years [14]. The constellation of cardiac changes attributable to endurance exercise training include mild eccentric left ventricular (LV) hypertrophy with concomitant right ventricular (RV) dilation, biatrial dilation, and enhanced diastolic function. In aggregate, these findings contribute to stroke volume augmentation and thus increased substrate delivery to peripheral tissue during exercise. This is one of several key adaptive mechanisms that contributes to supra-normal exercise capacity in trained individuals. But can you have too much of a good thing?

We previously conducted a study examining the impact of high volume / high intensity training on left ventricular mechanics, a term used to denote the process of tissue deformation, in a small cohort of competitive rowers [15]. Male collegiate athletes, all with significant prior exercise exposure, were studied with echocardiography before and after a 90-day period of intense team based rowing training. In this setting we saw increases in systolic fiber shortening in all regions of the left ventricle in each of the three cardinal strain vectors (radial, longitudinal, and circumferential) with one notable exception. Specifically, we documented relative functional decrements in systolic circumferential shortening. Though correlation analyses do not establish causality, it was noteworthy that the magnitude of septal dysfunction correlated tightly with the corollary increases in RV dilation. Thus, it appeared that the RV dilation attributed to training was associated with a decrement in LV septal function. Although explanations remain speculative, it seems plausible that exercise-induced RV remodeling leads to functional deterioration, perhaps a form of fatigue, within septal regions comprised of inter-digitating RV and LV fibers.

Although the clinical relevance of this finding remains unknown, several recent studies appear to be of direct relevance. Within the last year, two independent publications have documented cardiac

fibrosis in seasoned endurance athletes. Utilizing magnetic resonance imaging, Wilson and colleagues observed septal “hinge-point” (i.e., region of interface between the right and left ventricles) fibrosis in 4 of 12 veteran athletes (57 ± 6 years of age, 43 ± 6 years of training) and no evidence of scar among control groups of younger athletes and sedentary age matched people [7]. It is noteworthy that the presence of fibrosis was associated with the number of years of prior exercise training and the number of previously completed competitive endurance racing events. Subsequently, La Gerche et al used multi-modality imaging (echocardiography and magnetic resonance imaging) to examine biventricular structure, function, and fatigability in accomplished endurance athletes ($n = 39$) [8]. In this study, small groups of athletes were studied before and after long-distance events including marathon running, cycling, and triathlon. Post-event decrements in cardiac function, particularly of the right ventricle, suggested an element of cardiac fatigue. However, the most notable finding of this study was the presence of cardiac fibrosis in a small subset of these accomplished athletes. Myocardial fibrosis, confined in each case to the interventricular septum, was documented in 5 of these individuals and was associated with greater cumulative prior exercise exposure and more RV dilation. In aggregate, these recent studies suggest that repetitive exercise-induced cardiac fatigue may lead to fibrosis (permanent tissue damage) in a subset of experienced athletes. It must be emphasized that these observational, cross-sectional data do not establish causality and thus the above studies simply establish the fact that certain patterns of cardiac fibrosis have been observed in small, research cohorts. What do these findings mean and how do they impact the clinical care of the endurance athlete?

It is well established that while routine physical exercise reduces the risk of cardiovascular disease, it is not fully protective. This concept is most easily understood when one considers the interplay between exercise and atherosclerotic coronary artery disease. Numerous studies have shown that exercise is an effective treatment for coronary disease and reduces associated event rates. However, individuals with atherosclerosis are more likely to suffer a coronary event during the exercise that contributes to their longevity than during periods of inactivity [16]. This simple but important paradox illustrates the point that while exercise is good for

health, it is not completely protective. Our patients need to understand this paradox and must not fall victim to the belief that exercise, even very high levels of it, obviates the need for alternative risk factor reduction strategies. We may now also wish to acknowledge that there can be too much of a good thing in that high amounts of exercise may actually increase the likelihood of certain forms of heart disease.

Conclusion

We are continuing to accumulate evidence that long-term exposure to intense exercise may increase the incidence of certain cardiovascular conditions. This concept is increasingly recognized with respect to the atrial tachyarrhythmias, most notably atrial fibrillation which is a common and increasingly recognized problem among aging endurance athletes [17,18]. The recent studies by Wilson and La Gerche suggest that in addition, certain individuals may develop distinct patterns of cardiac fibrosis following years of endurance exercise. Thus, we are now beginning to appreciate that there may be a distinct form of cardiomyopathy attributable to “excessive” exercise. What factors dictate susceptibility to this condition and to what extent a cardiomyopathy of excessive exercise impacts morbidity and mortality remains completely speculative. At the present time, studies defining cardiac damage in athletes should be considered hypothesis generating and should serve as rationale for future study. Specifically, we need carefully designed, longitudinal studies of aging endurance athletes with serial phenotyping, physiologic provocation, careful observation to exclude alternative explanations for non-coronary disease related fibrosis (i.e., myocarditis), and attention to clinically relevant end-points.

While we await this work, it seems prudent to rely on the available data regarding the association between longevity and physical fitness when we are asked the question, “Should I train or not?” The links between living longer, living better, and physical fitness are clear and thus we should encourage high levels of physical exercise for our patients and our communities. It cannot be overemphasized that net risk-benefit ratio strongly favors a high-volume and intensity physically active lifestyle as there is incontrovertible evidence that longevity increases with physical fitness and that aging athletes appear to be less susceptible to disease than sedentary counterparts [19–21]. We should simultaneously be

aware that exercise, like all physiologic stimuli, probably behaves in a typical dose-response fashion in which an individual can reach levels that do more harm than good. Recognizing the patient who exercises excessively may be challenging and requires careful attention to subjective symptomatic reports and temporal exercise patterns. In clinical cardiovascular practice, lessons learned from the science of human performance including the need for dedicated rest and training periodicity may prove applicable to our patients and may be the best defense against the toxicity of excessive exercise. •

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The improvement of trimetazidine on exercise performance in ischemic heart disease

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Abstract

Ischemic heart disease (IHD) patients with a decreased exercise capacity have increased angina attack rate and poor quality of life (QOL). Conventional hemodynamic drugs show limited improvement in exercise performance. Therefore we need new drugs that may further improve exercise capacity. Trimetazidine (TMZ) exerts its anti-ischemic effect by reducing fatty acid oxidation and stimulating glucose oxidation, which induces more ATP production. Recent studies have demonstrated TMZ improve ejection fraction of the IHD patients, all these lead to a better exercise capacity and QOL.

Keywords: trimetazidine (TMZ); ischemic heart disease (IHD); exercise capacity; exercise performance; quality of life (QOL); left ventricular ejection fraction (LVEF).

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Introduction

Ischemic heart disease (IHD) is the first contributor of death and disability in many countries [1]. Although IHD mortality rates have declined over the past four decades in some developed countries, IHD remains responsible for about one-third of all deaths in individuals over age 35, and most of the survivors suffer from severe symptoms, limited exercise capacity, poor quality of life (QOL) [2]. As the data showed, the annual rate of hospital admission is about 15% to 20% in IHD patients with heart failure treated with conventional hemodynamic drugs [3]. Hence, there remains a need to identify new drugs that may further improve outcome especially symptoms, exercise capacity, and left ventricular (LV) function, which are closely linked to QOL and the main reasons of hospital admission.

TMZ has been shown to be an effective drug for the treatment of stable angina both alone or in addition to hemodynamic drugs. Recent studies have demonstrated that TMZ not only relief angina symptoms, but also improve ejection fraction of the IHD patients with left ventricular dysfunction (LVD), all these lead to a better exercise capacity and QOL [4-6].

TMZ is a metabolic modulator that inhibits a key enzyme in fatty acid oxidation—the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase—and shifts cellular energy substrate reference from fatty acids to glucose oxidation. A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the number of moles of ATP produced per mole of oxygen consumed is approximately 12% higher for glucose than for fatty acids [7]. Therefore,

unlike the conventional anti-anginal agents, which act by producing hemodynamic changes to restore balance between myocardial oxygen supply and demand, TMZ increases cellular tolerance to ischemia by inhibiting fatty acid metabolism and, secondarily, stimulating glucose metabolism [8,9].

The aim of the article is to review the TMZ efficacy on exercise capacity, LV function, and QOL in IHD patients.

Effect of TMZ on exercise capacity

Exercise capacity is the maximum amount of physical exertion that a patient can sustain. IHD patients with a decreased exercise capacity have an increased angina attack rate and poor QOL.

TMZ has a metabolic mode of action and it has been shown to preserve energy balance and prevent disturbance of ion homeostasis during ischemia. Results from studies demonstrated that TMZ significantly improved exercise tolerance in patients with stable angina when used either as monotherapy or when combined with β -blockers or calcium antagonists.

A multicenter, randomized, double-blind, placebo-controlled, international study involving 223 patients with stable angina pectoris (class II or III of the Canadian Cardiovascular Society [CCS] classification) showed that TMZ significantly improve patients' functional capacity, after 8 weeks of treatment, at trough. Time to 1mm ST segment depression was significantly increased by 44 seconds comparing with the placebo group ($p = 0.005$). A significant difference was also evidenced for the time to onset of angina pectoris ($p = 0.049$) and for the reason for stopping the exercise ($p = 0.02$) [10]. In addition, TMZ was well tolerated.

A study by Sisakian et al involved a total of 82 patients with ischemic cardiomyopathy who previously suffered a myocardial infarction. Results demonstrated that a therapeutic intervention with TMZ in conjunction with the standard therapy, over a three-month period, is associated with improved tolerance to physical activity, the tolerance to physical activity improved by 30.0 ± 20.7 m in the TMZ group vs. 2.0 ± 18.85 m in the control group ($P < 0.001$) [11].

TMZ improves functional capacity not only in IHD patients, but also in heart failure patients. A study by Belardinelli involving 116 IHD patients with LVD showed that peak VO_2 was significantly increased by

25% in the TMZ + exercise training (ET) group ($P < 0.001$) [12]. This result is the first to demonstrate that TMZ potentiates the beneficial effects of ET on functional capacity. TMZ potentiates the effects of ET on cardiovascular performance through its action on cellular metabolism and on the oxidative balance. Metabolic modulation contributes to the improvement in cardiac performance and LV function, which are both enhanced by aerobic exercise through different mechanisms.

Benefits of TMZ on exercise tolerance were further confirmed by meta-analysis of Agustín Ciapponi et al, which involved 1378 patients with stable angina from 23 studies. Results showed that TMZ significantly increased the time to 1mm ST segment depression [0.32 (0.15, 0.48)] [13]. These meta-analysis also demonstrated that TMZ could significantly improve exercise capacity both as monotherapy and when used in conjunction with selected hemodynamically active anti-anginal drugs.

Effect of TMZ on left ventricular ejection fraction

For patients with LVD, the improvement in left ventricular ejection fraction (LVEF) is likely the main factor determining the observed improvement of quality of life and exercise tolerance. As mention above, the conventional therapy efficacy is still far from satisfaction. Recently, more and more evidences showed that TMZ is the promising additional therapy for LVD.

In the study of Fragasso et al, 55 patients with heart failure (NYHA II-IV) were randomly allocated to either conventional therapy plus TMZ or conventional therapy alone. After 13 months treatment, TMZ significantly improved NYHA functional class compared with the conventional therapy ($p < 0.0001$), and significantly increased LVEF from 36% to 43% ($p = 0.002$), whereas LVEF was significantly decreased from 38% to 34% in conventional therapy group [14]. These results indicate that long-term TMZ therapy could improve left ventricular function, leading to a better exercise performance.

Although the mechanism of TMZ improving LV function has not been clear so far, there are some hypothesis focuses on "energy starvation" [15]. As well-established anti-ischemic effects in patients with coronary heart disease, TMZ stimulates glucose use and ATP production, and then ameliorates the "energy starvation" state by inhibiting free fatty acid oxidation,

which may finally translate into mechanical efficiency. Furthermore, several studies and meta-analysis [16] have also demonstrated that TMZ was equally effective in patients with HF of ischemic and non-ischemic origin. These data confirm the metabolic mode of action of TMZ. Indeed, heart failure is known to be the consequences of metabolic abnormalities. Therefore, efficacy of TMZ in these patients with heart failure and non-ischemic origin is a proof of the metabolic mode of action of TMZ. Besides the energy metabolic modulating effect, Tuunanen et al [17] found some extra cardiac metabolic effects of TMZ when treating patients with idiopathic dilated cardiomyopathy. Nineteen non-diabetic patients with idiopathic dilated cardiomyopathy were included and randomized into TMZ or placebo group on the top of standard medication. After 3 months follow-up, LVEF in TMZ group was significantly increased, and glucose homeostasis were improved as well as insulin sensitivity. These extra cardiac metabolic changes may indirectly improve myocardial glucose metabolism and glycolysis, amplifying the effects mediated by the decrease in FFA oxidation observed in the cardiac tissue.

A recent meta-analysis conducted by Junbo Ge demonstrated TMZ could reverse cardiac remodeling. The meta analysis involved 884 CHF patients in 16 ran-

domized controlled trials (RCTs) [18], and found that TMZ therapy was not only improve the left ventricular end-systolic diameter (WMD: -6.67 mm, $p < 0.0001$) and left ventricular end-diastolic diameter (WMD: -6.05 mm, $p < 0.0001$), but also increase of total exercise time (WMD: 63.75 seconds, $p < 0.0001$) (Fig. 1).

Our team carried out a trial to investigate the myocardial protection efficacy of TMZ in percutaneous coronary intervention (PCI) patients [19]. TMZ was given 30 minutes before procedure and continued for 4 weeks. Result showed LVEF in the TMZ group was significantly improved compared with placebo (66.6% vs. 63.0%, $p = 0.03$). The data also underlines the cardio protection effect of TMZ in LVD treatment, including protecting membrane from oxidative damage, blocking calcium overload, inhibiting inflammation and apoptosis, and improving endothelial function. Our data further confirm the adjunct of TMZ opens a new therapeutic window for PCI patients to improve LV function.

Effect of TMZ on quality of life

QOL predicts not only short-term but also long-term mortality in patients with IHD. Therefore the treatments of IHD should focus not only on improving life expectancy, symptoms, functional status, but also QOL.

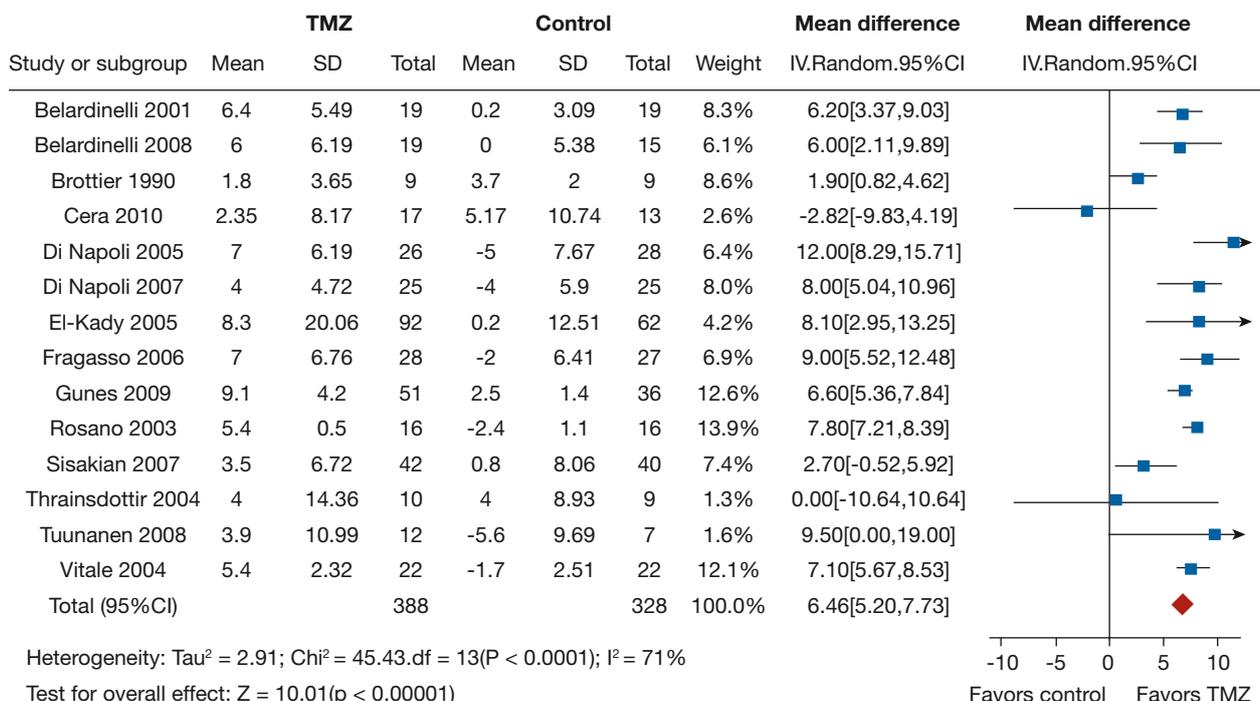


Fig. 1 Forest plots for left ventricular ejection fraction.

Available data showed that TMZ has a positive impact on QOL in patients with IHD. A RCT by Vitale et al aimed to assess the effects of TMZ in addition to standard cardiovascular therapy on QOL parameters in 62 elderly patients with IHD [20]. The overall assessment of QOL by a visual analog scale showed an improvement in patients allocated to TMZ at 6 months (from 4.1 ± 0.6 to 6.4 ± 0.8 , $P < 0.01$) and no changes in patients allocated to placebo (from 4.3 ± 0.7 to 4.2 ± 0.9 , $P > 0.05$). Physical QOL, evaluated by a MacNew Quality of Life After Myocardial Infarction questionnaire (MacNewQLMI), significantly improved in TMZ arm ($32\% \pm 5\%$ vs. $-1\% \pm 3\%$, $P < 0.01$). Social QOL evaluated by MacNewQLMI with TMZ compared with placebo also obtained similar results ($39\% \pm 4\%$ vs. $-2\% \pm 5\%$, $P < 0.01$). This study confirmed that in elderly patients with IHD TMZ improves clinical condition and QOL. Another study by Marazzi et al also evaluated the effects of TMZ on QOL in patients with ischemic dilated cardiomyopathy and got the similar results.

The effect of TMZ on reverse remodeling may explain its effect on QOL. The improvement in ventricular performance may cause a reduction in symptoms and an improvement in functional capacity and QOL. Another mechanism is the increase in muscle strength related to the improved hemodynamic conditions and in part could be related to a direct effect of TMZ on skeletal muscle.

TMZ improves clinical condition and QOL not only in IHD patients, but also in heart failure patients. A study by Fragasso et al [21] enrolled 55 patients with heart failure secondary to IHD, who were randomly allocated to conventional therapy plus TMZ or conventional therapy alone. QOL was assessed with two tests: visual analogue scale and LVD questionnaire (LVD-36) in order to measure the impact of LVD on daily life. The study demonstrated a significant decrease in LVD-36 score (from 18 to 15, $p=0.038$) in favor of TMZ. The improvement in LV function is likely the main factor determining the observed improvement of QOL including increased exercise tolerance and decreased NYHA functional class.

Conclusions

Exercise capacity and QOL becomes more and more important in IHD management. Available data strongly suggest that TMZ improves exercise performance, LV

function, and QOL in IHD patients and these benefits are possibly due to its metabolic mechanism. Therefore, the adjunct of a metabolic drug to conventional hemodynamic drugs should be used widely in these patients. •

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Life saving pre-participation athletic screening

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Abstract

Sudden cardiac death (SCD) of a young athlete is the most tragic event in sports. Competitive sports activity is associated with an increase in the risk of arrhythmic SCD in susceptible subjects with clinically silent cardiovascular disorders. Screening including 12-lead electrocardiogram (ECG) has been demonstrated to allow identification of athletes affected by malignant cardiomyopathies at a pre-symptomatic stage and leads to substantial reduction of SCD during sports. We report a case of a life-saving pre-participation cardiovascular evaluation in a young athlete.

Keywords: arrhythmogenic right ventricular cardiomyopathy; electrocardiogram; pre-participation screening; implantable cardioverter defibrillator; sports cardiology.

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Case Report

Case report

A 23-year-old male competitive soccer player was referred for routine pre-participation cardiovascular screening, based on family and personal history, physical examination and 12-lead electrocardiogram (ECG) as first-line evaluation. The athlete was completely asymptomatic and he had unremarkable family history and physical examination findings. Standard ECG showed depolarization/repolarization abnormalities and ventricular arrhythmias that were highly suggestive of arrhythmogenic right ventricular cardiomyopathy (ARVC) (Fig. 1A). There were typical negative T-waves in inferior and anterolateral precordial leads as well as isolated premature ventricular beats with a left bundle branch block (LBBB) and superior axis morphology. Moreover, there was a non-specific right intraventricular conduction defect in the form of localized slowing of the terminal part of QRS complex in V1 and V2 leads. Because of the abnormal ECG features, the patient underwent further diagnostic work-up to achieve a definitive diagnosis of ARVC. Laboratory exams were normal. During 24-hour (12 lead-ECG) Holter monitoring, the patient had frequent premature ventricular beats ($\approx 12,000/24$ hours) with two morphologies (LBBB/superior axis [prevalent] and LBBB/inferior axis) and, most important, he experienced exercise-dependent non-sustained ventricular tachycardia (Fig. 1B). Transthoracic echocardiogram revealed moderate right ventricular (RV) dilatation with akinesia of the anterolateral wall and hypokinesia of the posterobasal wall; right ventricular outflow tract (RVOT) dilatation (RVOT/aortic diameter ratio 1.38); mild dilatation of the left ventricle with no wall motion abnormalities;

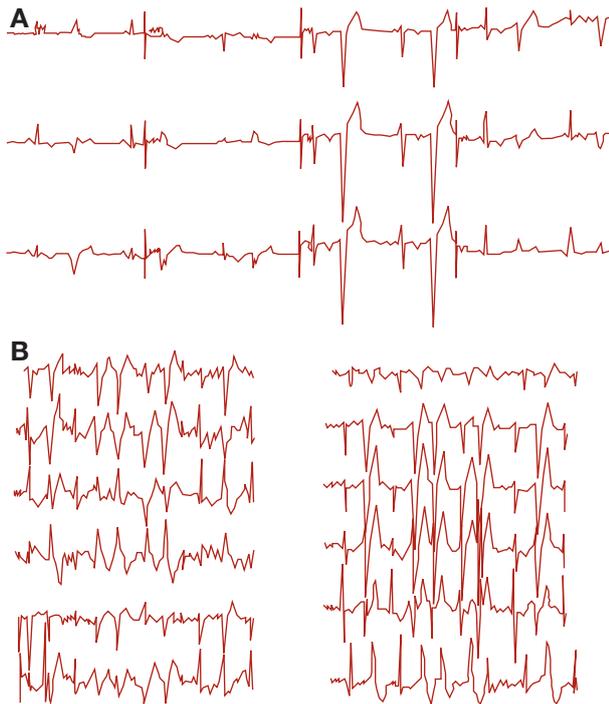


Fig. 1 **A)** 12-lead electrocardiogram showing inverted T-waves in leads II, III, aVF and V1-V6 and delayed S-wave upstroke of QRS complex in V1 and V2. Note the isolated premature ventricular beats with a left bundle branch block and superior axis pattern. **B)** 24-hour-12 lead-electrocardiogram Holter monitoring showing a non sustained ventricular tachycardia (4 beats) with left bundle branch block/superior axis pattern.

and normal flow across all cardiac valves. Contrast-enhanced cardiac magnetic resonance (CMR) demonstrated the presence of RV aneurysms and large fibrofatty scar of the anterolateral wall (Fig. 2). The patient then underwent invasive 3-dimensional endocardial voltage mapping using CARTO system (Biosense Webster, Daimond Bar, California) that showed a large RV electroanatomical scar in the anterolateral region, which was concordant with CMR findings. RV endomyocardial biopsy displayed extensive fibrofatty myocardial replacement with islands of degenerating residual myocytes.

In the light of the clinical data (major ECG, arrhythmic, and morpho-funtional abnormalities) and according to International Task Force diagnostic criteria [4], the patient was diagnosed with “definite ARVC.” Accordingly, he was disqualified from competitive sport activity and was advised to refrain from any physical exercise. In addition, he was prescribed beta-blocker therapy (atenolol 50 mg per day), which was proven to be successful in preventing effort-induced ventricular arrhythmia by a control stress testing.

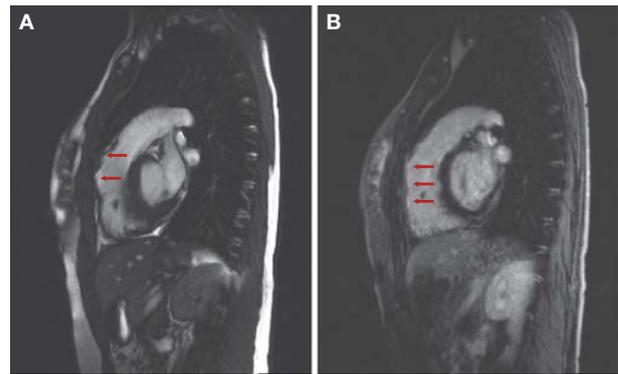


Fig. 2 Findings of contrast-enhanced cardiac magnetic resonance (MR) **A)** Systolic frame of cine MR image of right ventricular (RV) outflow tract showing ventricular aneurysms of anterolateral wall (arrows). **B)** Post-contrast sequences showing the presence of late gadolinium enhancement (bright signal intensity) in the RV outflow tract (arrows), that is the same region of ventricular aneurysms.

Unfortunately, beta-blockers therapy was not tolerated because of symptomatic sinus bradycardia (30–35 bpm) and was withdrawn. The athlete was then scheduled for prophylactic implantation of defibrillator (ICD). One month after the ICD implant, the patient reported falling off his mountain bike without loss of consciousness. On interrogation of the device at the time of the event, it was demonstrated that the athlete had experienced an episode of ventricular flutter that was appropriately detected by the device and successfully interrupted by shock therapy (Fig. 3).

Discussion

The present article reports on a representative case of “life-saving” pre-participation screening. The diagnosis of ARVC in the young athlete resulted in the prevention of SCD not only because of disqualification from competitive sports but also thanks to the subsequent close follow-up and clinical management. The former athlete became a patient who entered a clinical program of risk stratification and prophylactic ICD implantation for prevention of SCD.

Pre-participation screening

A nationwide program for screening young competitive athletes has been implemented in Italy since 1982 [1–3]. The flow chart of the Italian protocol of cardiovascular pre-participation screening is reported in Fig. 4 [2]. The long-term Italian experience demonstrated that pre-participation ECG identifies athletes affected by potentially lethal cardiomyopathies such as hypertrophic cardiomyopathy (HCM) and ARVC



Fig. 3 Implantable cardioverter defibrillator stored electrocardiogram showing the episode of ventricular flutter (300 bpm) that was appropriately detected by the device and interrupted by a shock (arrow) of 34.7 joules.

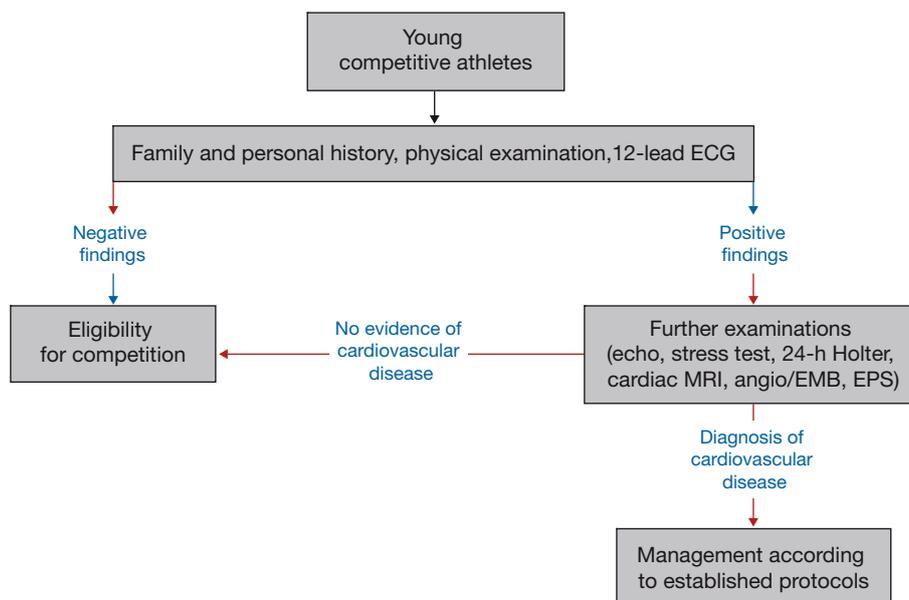


Fig. 4 Young competitive athletes are defined as individuals 12 to 35 years of age who are engaged in a regular fashion in exercise training as well as participating in official athletic competitions. First-line examination includes family history, physical examination, and 12-lead electrocardiography (ECG); additional tests are requested only for subjects who have positive findings at the initial evaluation. Angio/EMB contrast angiography/endomyocardial biopsy, EPS electrophysiologic study with programmed ventricular stimulation, MRI magnetic resonance imaging. Modified from Corrado et al [4].

[1,2]. Twenty-four years after screening implementation, the annual incidence of SCD in screened athletes decreased by 89%, while the incidence of SCD in unscreened population remained unchanged. Most of the reduction was attributable to fewer deaths from HCM and ARVC [2]. The importance of identification by ECG screening of asymptomatic athletes with cardiovascular diseases relies on the concrete

possibility of SCD prevention by lifestyle modification, including restriction of competitive sports activity and concomitant prophylactic treatment by antiarrhythmic drugs, beta-blockers and ICD therapy [4]. We previously reported that athletes who did not obtain eligibility for competition because of cardiovascular reasons have a good long-term clinical course thanks to the subsequent medical management [1].

ARVC

ARVC is an inheritable heart muscle disease characterized pathologically by fibrofatty replacement of the RV myocardium [5]. Molecular genetic studies showed that ARVC is a desmosomal disease resulting from genetically defective cell-adhesion proteins such as plakoglobin, desmoplakin, plakophilin-2, desmoglein-2, and desmocollin-2 [5–7]. Clinical manifestations are related to electrical instability, including either ventricular tachycardia (VT) of RV origin or ventricular fibrillation (VF), which may lead to SCD, mostly in young people or athletes [5,8]. Ventricular arrhythmia worsens during or immediately after exercise and participation in competitive athletics is associated with an increased risk for SCD [5,8–10]. The disease affects men more frequently than women and becomes clinically overt most often in the second or third decade of life. Clinical diagnosis of ARVC is often difficult because of the nonspecific nature of the disease and the broad spectrum of phenotypic manifestation, ranging from severe to concealed forms. In 1994 an International Task Force proposed criteria for the clinical diagnosis of ARVC based on the presence of major and minor criteria encompassing electrocardiographic, arrhythmic, morpho-functional, histopathologic, and genetic factors [11]. These Task Force diagnostic criteria have been revised in 2010 [12]. The most important therapeutic objective in ARVC is to prevent arrhythmic sudden death. The ICD is the most effective tool against arrhythmic SCD, although antiarrhythmic drugs and catheter ablation may play a role for treatment of non life-threatening arrhythmia [5,13].

SCD during sports

Athletes have a 5.4 times greater risk to die suddenly from ARVC than sedentary population [9]. The arrhythmogenic effect of exercise was reproduced by animal model study of genetically altered mice subjected to endurance training [14].

The most frequent clinical manifestations of ARVC consist of ECG depolarization/repolarization changes mostly localized to right precordial leads, arrhythmias of RV origin and global and/or regional morphologic and functional alterations of the right ventricle [5,8,11,12]. The disease course is often silent and SCD can be the first clinical manifestation. Thus, the challenge is the early identification of still asymptomatic individuals on the basis of ECG abnormalities [15,16]. Final diagnosis relies on visualization of morphofunc-

tional RV abnormalities by current imaging techniques (such as echocardiography, angiography, or cardiac magnetic resonance) and, in selected cases, by histopathologic demonstration of fibrofatty substitution at endomyocardial biopsy [5,8,17].

It is noteworthy that more than 80% of athletes who die from ARVC have ECG changes or ventricular arrhythmias [1,2,10]. Most common ECG abnormalities include right precordial inverted T-waves (beyond lead V1) in 88%, right precordial QRS duration >110 msec in 75%, and ventricular arrhythmias with a left bundle branch block pattern, mostly in the form of isolated/coupled premature ventricular beats or non-sustained ventricular tachycardia, in 75%. These ECG abnormalities could raise the suspicion of an underlying heart muscle disease at pre-participation evaluation and lead to further testing for a definitive diagnosis. Right precordial T-wave inversion (beyond V1) appears to be the most sensitive clinical marker for the presence of a potentially fatal ARVC in apparently healthy young competitive athletes [5,10].

According to recommendations for sports eligibility [18], athletes with clinical diagnosis of ARVC are excluded from all competitive sports. This recommendation is independent of age, gender, and phenotypic appearance and does not differ for those athletes without symptoms, or treatment with drugs, or interventions with surgery, catheter ablation, or implantable defibrillator.

ICD therapy in ARVC

Therapeutic options in ARVC patients include beta-blockers, antiarrhythmic drugs, catheter ablation, and ICD [13]. Although ICD confers optimal protection against SCD in ARVC patients, the significant rate of inappropriate interventions and complications, as well as the psychological repercussions mostly in the younger age group, argue strongly against indiscriminate device implantation [7]. The best candidates for ICD therapy are patients with prior cardiac arrest and those with VT with hemodynamically unstable VT (i.e., associated with syncope or shock); syncope which remains unexplained after exclusion of non-cardiac causes and vaso-vagal mechanisms is also considered a valuable predictor of sudden death and represents “per se” an indication for ICD implantation [5,19,20]. In this high-risk group of patients, the rate of appropriate ICD intervention against life-threatening ventricular tachyarrhythmias (that in all likelihood

would have been fatal in the absence of shock therapy) is approximately 8–10% per year and the estimated mortality reduction at 36 months of follow-up ranges from 24–35% [5,19]. On the contrary, ICD implantation for primary prevention in the general ARVC population seems to be unjustified. As indicated by a recent multicenter study on prophylactic device implantation in ARVC patients with no sustained VT or VF, asymptomatic probands and relatives do not benefit from ICD therapy, regardless of familial sudden death or inducibility at programmed ventricular stimulation [20]. This patient cohort carries a low arrhythmic risk over a long-term follow-up (ICD intervention rate < 1 per year), in addition to a significant rate of device-related complications and inappropriate discharges. Patients with well-tolerated sustained VT or non-sustained VT on Holter or exercise testing have an intermediate arrhythmic risk (ICD intervention rate ~1–2% per year). In this patient subgroup, the decision for ICD implantation needs to be individualized. Our young athlete with ARVC received an ICD because of demonstration of non-sustained VT which, most important, occurred during effort. This is a recognized sign of malignant arrhythmic outcome [5,8–10].

Conclusions

The present case highlights the importance of ECG screening in identifying asymptomatic athletes with genetic cardiomyopathy or channelopathies because of the concrete possibility of SCD prevention by lifestyle modification, including restriction of competitive sports activity and concomitant prophylactic treatment by beta-blockers and/or implantable cardioverter-defibrillator therapy. •

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Effects of performance-enhancing drugs on cardiac structure and energy metabolism

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Abstract

Due to their potential to increase strength, athletes may consume performance-enhancing drugs (PEDs) such as anabolic androgenic steroids (AAS) and human growth hormone (GH). Despite the controversies surrounding the use of AAS and human GH, the chronic regimes and doses consumed for performance enhancement are markedly higher than those used acutely in clinical situations (with respect to compounds approved for therapeutic use), and may have adverse effects on the myocardium. These include increases in cardiac mass, though whether this hypertrophy is physiological or pathological in nature remains unclear. Regardless, cardiac hypertrophy is associated with secondary changes in cardiac energy metabolism that may contribute to cardiac dysfunction and the progression towards heart failure. As the misuse of PEDs may also result in sudden cardiac death, a better understanding of PED-induced cardiac hypertrophy and energy metabolism is required.

Keywords: performance-enhancing drugs; anabolic androgenic steroids; human growth hormone; left ventricular hypertrophy; cardiac energy metabolism.

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Introduction

The clandestine use (and abuse) of performance-enhancing drugs (PEDs) by athletes is rooted in the expectation that these substances increase strength and athletic performance, and thus have the potential to provide an advantage (albeit clearly unfair) over other competitors in the field. Even though the ability of PEDs to increase athletic performance is controversial, these compounds are used by both competitive and recreational athletes. However, the use of these compounds is not benign, as they can pose serious adverse risks to health, including those pertaining to the cardiovascular system. Indeed, enhanced physical performance must be met by elevated cardiac workload and energy demand. As such, PEDs may directly and/or indirectly influence cardiac energy metabolism. Furthermore, PEDs are associated with an increased risk of left ventricular (LV) hypertrophy. As alterations in cardiac energy metabolism have been demonstrated to contribute to the development of cardiovascular disease [1,2],

and since the hypertrophied heart itself undergoes metabolic maladaptations [1], the potential risks of PED use/abuse on cardiovascular health are of high clinical relevance. Although the list of compounds utilized as PEDs is vast, and their effects numerous, this article will be limited to the discussion of the potential effects of anabolic androgenic steroids (AAS) and human growth hormone (GH) on cardiac structure and energy substrate metabolism.

AAS and human GH as PEDs

AAS are derivatives of testosterone, which have been chemically modified such that anabolic effects (increased protein synthesis/decreased protein degradation, increased lean body mass/muscle mass) predominate relative to androgenic (masculinizing) effects. Clinically relevant AAS include nandrolone, oxandrolone, oxymetholone, and stanozolol. A number of clinical trials have demonstrated that short-term treatment with AAS is relatively safe, and has utility following major trauma, surgery, prolonged periods of immobilization, and various wasting conditions, settings where AAS attenuate protein loss in otherwise catabolic disease states [3]. It should be noted that a large number of testosterone derivatives have been synthesized (>1000), which has resulted in a market for illicit, “designer” AAS [4]. The chronic abuse of these compounds has serious adverse effects. With respect to the cardiovascular system, AAS abuse has been associated with abnormal lipid profiles (i.e. increased LDL/decreased HDL cholesterol), elevations of blood pressure, LV hypertrophy, acute myocardial infarction, and sudden cardiac death [5,6]. Of these changes, LV hypertrophy may have prominent effects on cardiac energy metabolism (see below) in the setting of chronic AAS abuse.

Human GH is secreted from the anterior pituitary, and circulates predominantly as a 22 kDa peptide. GH has both direct and indirect effects (mediated by insulin-like growth factor I) in a variety of tissues. With respect to potential performance enhancing effects, GH increases cellular amino acid uptake, stimulates skeletal and muscle growth (increases lean body mass), decreases adiposity, and increases heart rate and cardiac output [7]. However, it should be noted that GH promotes a diabetic-like profile of catabolic metabolism, as it increases circulating free fatty acid (FFA) levels, while decreasing skeletal muscle insulin-sensitivity [7]. Interestingly, acute treatment (15 days) with recombinant human

GH increases stroke volume and contractility in experimental heart failure secondary to coronary artery ligation [8]. Although not a consistent finding, a number of small clinical studies have also reported beneficial effects of GH treatment in the settings of non-ischemic [9,10] and ischemic heart failure [11]. On the surface, these findings appear to suggest that acute GH treatment may be cardioprotective. However, chronic GH abuse may elicit pathological alterations in cardiac structure and metabolism, exemplified by hypertrophic cardiac remodeling in the setting of acromegaly (GH excess).

Cardiac energy metabolism in the healthy heart

In the normal healthy heart, virtually all (~95%) ATP generated arises from mitochondrial oxidative phosphorylation, with the remainder derived from glycolysis. In cardiac muscle, fatty acids account for 60–80% of oxidative energy metabolism, while carbohydrates such as glucose and lactate account for the remaining 20–40%. Despite producing more ATP than carbohydrates, fatty acids are not as oxygen-efficient, requiring ~10% more oxygen to produce an equivalent amount of ATP [12]. In addition, fatty acids directly inhibit the oxidation of carbohydrates through a phenomenon termed the “Randle cycle.” This uncouples glycolysis from glucose oxidation, which increases proton production and reduces cardiac efficiency [12].

If the demands of the heart are increased, such as following exercise, the healthy heart can increase LV contractile power and myocardial oxygen consumption 4–6 fold above resting values [13]. Although an acute increase in cardiac workload generally increases myocardial fatty acid uptake and β -oxidation, the relative increase is greater for carbohydrates (glucose and lactate) following exercise, or β -adrenergic stimulation and elevated afterload [13]. The *in vivo* response is highly dependent on the arterial concentrations of energy substrates, as an increase in arterial lactate during exercise markedly enhances its myocardial uptake at the expense of FFAs [14]. Conversely, with prolonged moderate intensity exercise (>30 min), increased adipose tissue lipolysis and the subsequent elevation in plasma FFA levels enhances myocardial FFA uptake and β -oxidation [15].

Cardiac metabolism in the hypertrophied heart

While physiological hypertrophy and its associated metabolic changes are adaptive to cardiovascular

function, the metabolic alterations following pathological hypertrophy are maladaptive and may contribute towards the progression to overt heart failure (see [1] for in depth review of energy metabolism and its alterations in the hypertrophied heart). These metabolic changes include a reversion to a fetal phenotype of energy substrate metabolism. Specifically, glycolysis increases, while fatty acid β -oxidation decreases and glucose oxidation rates either slightly increase or remain unaltered in response to cardiac hypertrophy [16,17]. Despite these alterations in oxidative energy metabolism, overall tricarboxylic acid cycle activity remains normal, due in part to a marked increase in anaplerotic flux from glycolytically-derived pyruvate (via flux through malic enzyme) in the hypertrophied heart [18]. Another key factor separating physiological from pathological hypertrophy, and potentially contributing to their associated metabolic differences may be due to angiogenesis. Physiological hypertrophy due to exercise is accompanied via matched increases in vascularity such that the myocardium is sufficiently oxygenated, whereas pathological hypertrophy is not accompanied via a similar increase in vascularity, resulting in tissue hypoxia, which likely contributes to the elevation in glycolytic rates [19].

PEDs & LV hypertrophy

Whereas the therapeutic use of AAS and GH is usually aimed at replacement therapy, and utilizes low doses, abuse of these substances for the purposes of performance enhancement employs doses that can be much greater than those utilized clinically (e.g., use of AAS as performance enhancing drugs can be 40–100-fold greater than therapeutic doses [4]), or the use of untested/novel designer compounds. Due to ethical considerations, the effects of such dosing regimens on aspects of cardiac function (for that matter human health) cannot be assessed using randomized placebo controlled trials. However, the adverse effects of chronic AAS use on cardiac structure and function may be garnered from case reports, as well as non-blinded trials with AAS users, while those of chronic GH use may resemble adverse cardiac remodeling observed in acromegaly (chronic GH excess).

Although not a consistent finding, a number of reports provide echocardiographic evidence of concentric hypertrophy in AAS users (See [5] for review).

While concentric hypertrophy can initially represent physiological hypertrophy, its maladaptive characteristics in the setting of AAS use are evidenced by diastolic dysfunction [20,21], which can also occur in the absence of overt hypertrophy [22], resulting in impaired ventricular relaxation and filling at normal pressures. Clinically, cardiac hypertrophy and diastolic dysfunction, which eventually progress to systolic heart failure are cardinal pathologies observed in growth hormone excess [23]. A potential common underlying mechanism of cardiac hypertrophy in response to AAS and GH may involve activation of the renin-angiotensin aldosterone system [24]; however, this is not firmly established. Regardless of the potential trigger(s), the mediators of cardiac hypertrophy secondary to chronic AAS or GH abuse likely involve one or more of the complex protein kinase cascades implicated in pathological cardiac hypertrophy [25]. Cardiac hypertrophy itself can progress to heart failure, and hypertrophy-induced alterations in cardiac energy metabolism accompany this progression as described above.

Concluding remarks

Despite the controversies surrounding the use of PEDs to gain competitive advantages, their use and misuse will likely continue amongst both competitive and recreational athletes. However, consumption for performance enhancement involves the use of very high doses, or in other situations the use of “designer” compounds. These facets of PED use may predispose to numerous adverse effects, including cardiac hypertrophy and secondary changes in cardiac energy metabolism, although the data is equivocal as to whether PED-induced LV hypertrophy is truly pathological in nature. In addition, individuals utilizing PEDs are for most part also engaged in regular exercise training regimens. How PEDs and differing exercise training regimens interact and affect cardiac structure, metabolism, and function is not well-characterized. Furthermore, direct assessments of cardiac energy metabolism in response to PEDs are few, illustrating the need to improve our understanding in this area. •

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Clinical assessment of revascularized patients

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The use of noninvasive stress testing for the diagnosis and prognostic assessment of chronic angina patients is well established [1,2] and represents a determinant factor in the selection of treatment strategy [3]. Contrarily, after coronary revascularization (both percutaneous and surgical), there is lack of evidence to support clinical decision-making in the same population set.

Previous trials have consistently reported that, following coronary revascularization, many patients suffer recurrent ischemia [4,5], a finding associated with adverse outcome [6,7]. Nonetheless, clinical assessment by means of stress testing is considered inappropriate within 2 years after percutaneous coronary intervention (PCI) and within 5 years after coronary artery by-pass grafting (CABG) [8–10]. Indeed, following revascularization, besides a high rate of positive test results in patients with patent coronary arteries [10,11], there is a lack of evidence that repeated revascularization would change the course of the disease or patient outcomes.

Harb et al [12] addressed the issue of routine stress echocardiography (SE) in asymptomatic patients following coronary revascularization. Although only 1158 (55%) had completely normal SE, of a total of 2105 patients, clear signs of ischemia on SE were diagnosed in 262 patients (13%). Patients with recurrent ischemia had higher mortality compared with those without ischemia (8.0% vs 4.1%; $p = 0.03$; [HR], 2.10; 95% CI, 1.05-4.19; $P=0.04$) and, repeat revascularization (performed in 33% of patients with ischemia) did not significantly improve survival. The authors concluded that, careful consideration is warranted before the screening of asymptomatic patients is considered appropriate at any stage after revascularization. Similarly, the concept of the “uselessness of stress testing after coronary revascularization” was highlighted in the accompanying editorial.

The lack of favorable mortality outcomes is considered a mainstay finding from this study. However, why do these results generate such a pronounced reflection? Were we not aware of similar findings from other population studies? Indeed, it is now well accepted that coronary revascularization in chronic settings improves quality of life but has little or no impact on prognosis [4,13].

Screening tests are adopted with the hope of identifying and resolving coronary obstructions electively. In post-revascularized patients this would include surveillance for restenosis, graft patency, and completeness of revascularization, all deemed causes of ischemia recurrence. However, following revascularization, the rate of positive tests with no need for repeat revascularization due to patent coronary artery is particularly high [10]. Accordingly, in a cohort

of 220 highly selected post-revascularized patients we found that more than a third presented with myocardial ischemia that could not be justified by the above stated causes of recurrency [14]. The study by Harb et al adds that, even when revascularization is feasible, this will not change the outcomes of persistently ischemic patients. Taken together, it becomes clear that there is a flaw somewhere in the model of myocardial ischemia and these findings call for the need for a better understanding. Paradoxically, the recommended attitude is to avoid performing stress testing in asymptomatic post-revascularized patients. Will we ever stop contenting ourselves with burying the head in the sand and conducting a “pretend-not-to-see” policy? •

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ATP

Adenosine-5'-triphosphate (ATP) is a multifunctional nucleoside triphosphate that acts as the molecular unit of currency in intracellular energy transfer. The primary objective of intermediary metabolism in living organisms is to maintain a steady supply of ATP required for growth, reproduction, and responding to the stresses (i.e., starvation, exercise) associated with daily living.

Dyslipidemia

Dyslipidemia is an abnormal amount of lipids (i.e., fatty acids and/or cholesterol) in the blood. In developed nations this is primarily an elevation in plasma lipids often resulting from diet and lifestyle choices.

Endurance

Endurance is often used interchangeably with the term "stamina" and represents the ability of individuals to exert themselves and remain active over a duration of time. It may also include the individual's ability to withstand and recover from the fatigue of exertion.

Fatty acids

Fatty acids are a group of molecules that consist of a carboxylic acid with hydrocarbon chains of varying lengths. Most naturally occurring fatty acids are synthesized from acetate, as such contain even numbers of carbon atoms, which can be saturated with hydrogen (i.e., the molecule is devoid of carbon-carbon double bonds), or unsaturated to varying degrees (i.e., the molecule contains carbon-carbon double bonds). Fatty acids represent an important energy substrate for cardiac energy metabolism.

Genotype/Phenotype

Genotype represents the inherited instructions that an organism carries within its genetic code, whereas phenotype represents the observable characteristics of that organism, which is often determined via the interaction between that organism's genotype with the environment.

Hypertrophy

In human physiology, hypertrophy is the increase in the volume/size of an organ or tissue due to the enlargement of the individual cells making up that organ. For example, exercise often induces hypertrophy of the heart due to stretching of ventricular myocytes in order to pump a larger volume of blood.

Insulin resistance/insulin sensitivity

Insulin resistance is characterized by the failure of insulin to mediate its metabolic actions in tissues that express the insulin receptor. As the primary role of insulin is to stimulate glucose uptake into insulin sensitive tissues (such as skeletal muscle, heart, and adipose tissue), insulin resistance often results in hyperglycemia as insulin fails to stimulate glucose uptake into these tissues. Insulin sensitivity represents how effectively insulin is able to stimulate glucose uptake into its target tissues.

Ketones

Ketones are a group of molecules that consist of a carbonyl group (C=O) bonded to two carbon atoms. In most mammals ketones are formed in the liver from a reaction initiated by the enzymatic condensation of 2 molecules of acetyl-CoA. Ketones (e.g., acetoacetate) are transported in the plasma to extrahepatic tissues where they can be oxidized in the tricarboxylic acid cycle. Ketone bodies are overproduced during starvation, and in the setting of diabetes.

MVO₂

Mixed venous oxygen saturation (MVO₂) measures the end result of oxygen delivery and consumption at the tissue level. With regards to the heart MVO₂ can be calculated according to the Fick principle, utilizing the arteriovenous oxygen difference and coronary flow rates, and reflects cardiac oxygen consumption where an increase in MVO₂ indicates increased oxygen consumption.

Randle Cycle

The Randle Cycle is a metabolic phenomenon characterized via substrate competition between carbohydrate (glucose) and fatty acids for entry into oxidative pathways (the Krebs Cycle) for subsequent energy metabolism. As the oxidation of one substrate increases, it results in decreased oxidation of the competing substrate.

Sarcolemma

The sarcolemma (i.e., sarcolemmal membrane) describes the phospholipid bilayer that surrounds striated muscle cells, and functions as a selective permeability barrier. •