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## Cardiac damage in athlete's heart: When the "supernormal" heart fails!

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### Abstract

Intense exercise may cause heart remodeling to compensate increases in blood pressure or volume by increasing muscle mass. Cardiac changes do not involve only the left ventricle, but all heart chambers. Physiological cardiac modeling in athletes is associated with normal or enhanced cardiac function, but recent studies have documented decrements in left ventricular function during intense exercise and the release of cardiac markers of necrosis in athlete's blood of uncertain significance. Furthermore, cardiac remodeling may predispose athletes to heart disease and result in electrical remodeling, responsible for arrhythmias. Athlete's heart is a physiological condition and does not require a specific treatment. In some conditions, it is important to differentiate the physiological adaptations from pathological conditions, such as hypertrophic cardiomyopathy, arrhythmogenic dysplasia of the right ventricle, and non-compaction myocardium, for the greater risk of sudden cardiac death of these conditions. Moreover, some drugs and performance-enhancing drugs can cause structural alterations and arrhythmias, therefore, their use should be excluded.

**Key words:** Athlete's heart; Cardiac damage; Fibrosis; Intense exercise; Arrhythmogenic dysplasia of the right ventricle; Atrial fibrillation; Doping; Anabolic-androgenic steroids; Hypertrophic cardiomyopathy

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**Core tip:** Athlete's heart is a physiological condition that in some cases can simulate pathological disease,

sometimes due to the use of doping drugs. Furthermore, exercise can induce atrial dilation and arrhythmias. Our objective is to analyze the current literature and to review the most important changes in the heart of athletes, from the different molecular pathways to the structural anomalies.

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## INTRODUCTION

High-intensity exercise training leads to morphological, functional, and electrical remodeling of the heart, which are included in the "athlete's heart", characterized by increased left ventricular mass (LVM), cavity dimensions and wall thickness<sup>[1]</sup>. Athletes with left ventricular (LV) hypertrophy generally have normal cardiac function and normal systolic and diastolic function<sup>[2]</sup>. Athletes exhibit an improvement in myocardial diastolic indices and supernormal LV diastolic function<sup>[3]</sup>. Recent studies have documented decrements, especially in right ventricular (RV) function, during intense endurance exercise<sup>[4,5]</sup>. Actual evidence suggests that there may be some overlap between physiological and pathological conditions, such that a modest amount of fibrosis may be present in cardiac remodeling associated with lifelong endurance training and then acts as a substrate for arrhythmias<sup>[6]</sup>.

Our objective is to describe the mechanisms of cardiac remodeling in athletes and to delineate the most important differences, from the molecular mechanisms to the structural changes, between athlete's heart and pathological conditions, taking into account the most important cardiomyopathy, arrhythmias and the abuse of performance-enhancing drugs.

## PHYSIOLOGICAL VS PATHOLOGICAL CARDIAC HYPERTROPHY: FROM PHYSICAL PRINCIPLES TO MOLECULAR MECHANISMS

Cardiac hypertrophy is an adaptive response to the increased cardiac loading that normalizes wall stress, according to Laplace relationship (Figure 1). Unfortunately, long-term maladaptive remodeling of reactive hypertrophy in various cardiovascular diseases (*e.g.*, valvular heart disease, myocardial ischemia, coronary artery disease, hypertension, and cardiomyopathy) is associated with gradual ventricular dilation, due to loss of myocytes and cardiac fibrosis<sup>[7]</sup>. Physiological hypertrophy, such as athlete's heart, is typically not associated with myocyte

death, although recent studies have shown myocardial damage during intense exercise and RV inflammation and fibrosis in long term endurance athletes<sup>[4,8]</sup>. The shift from compensated pathological hypertrophy to failure of myocardium includes cellular and molecular events, such as myocyte death, with three different mechanisms: Apoptosis, necrosis and autophagic cell death<sup>[9,10]</sup>. Cardiomyocyte replacement and myocardial fibrosis are representative of all types of pathological hypertrophy and proceed along with functional decompensation. To explain fibrosis and necrosis in athlete's heart, interesting is the "ischemic core" hypothesis: Hypertrophic cardiomyocyte becomes ischemic when his surface exceeds the distance across which oxygen can diffuse down its concentration gradient from adjacent capillaries, with contractile depression and cellular death<sup>[11]</sup>. Physiological hypertrophy is associated with a normal or increased number of myocardial capillaries, due to the activation of VEGF pathway<sup>[9]</sup>. Akt is a serine/threonine protein kinase responsible for the cellular growth in multiple cell types, which can be activated by exercise. Recent data suggest that Akt pathway might be implicated both in physiological and pathological cardiac growth. In animal models, myocardial expression of Akt pathway caused reversible hypertrophy after 2 wk of strenuous exercise, but an irreversible cardiomyopathy with decreased capillary density and fibrosis after 6 wk of intense training. It seems that myocardial angiogenesis is more intense in the acute phase of heart hypertrophy but insufficient in the advanced phase: Excessive "physiological" hypertrophy might be associated with poor angiogenesis and consequently with heart failure<sup>[12]</sup>.

Autocrine and paracrine triggers are released in response to hemodynamic overload, and definite substances are preferentially released for pathological or physiological stimuli. Insulin like growth factor 1 (IGF1) is released in the course of postnatal development and during exercise training and is increased in swim-trained rats and in veteran athletes compared with controls<sup>[13]</sup>, whereas elevated levels of angiotensin II (Ang II), catecholamine and endothelin-1 (ET-1) were observed in pathological hypertrophy and in heart failure subjects<sup>[14]</sup>. IGF1 promotes the PI3K-Akt molecular pathway to induce physiological cardiac hypertrophy, whilst the mitogen activated protein kinase (MAPK) pathway and calcineurin system are activated by Ang II and ET-1 in pathological hypertrophy (Table 1)<sup>[15]</sup>.

In conclusion, familial hypertrophic cardiomyopathy<sup>[16]</sup> is associated with sarcomeric protein mutations, such as cardiac troponin I or T,  $\beta$ -MHC,  $\alpha$ -MHC, myosin light chain,  $\alpha$ -tropomyosin, titin, and actin, with loss of contractile filaments and proteins of sarcomeric skeleton<sup>[17]</sup>.

## CARDIOMYOCYTE DAMAGE DURING INTENSE EXERCISE

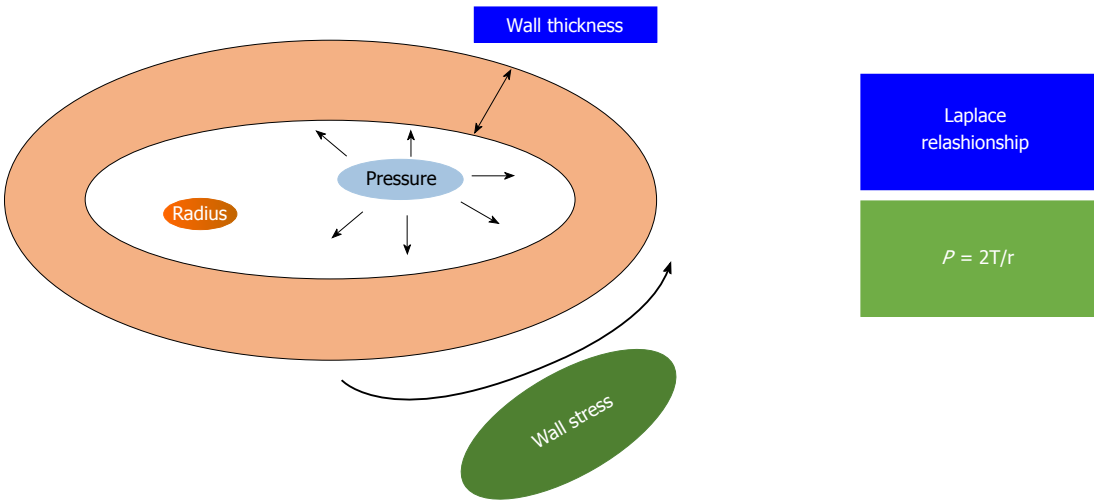
After intense exercise, acute increases in troponin (cTn) and B-type natriuretic peptide have been detected in



**Table 1** Differences in between physiological and pathological hypertrophy

Physiological hypertrophy	Pathological hypertrophy
Angiogenesis, release of VEGF	Perivascular fibrosis and inflammation
Activation of IGF-1 pathway (IGF-1- > PI3K- > Akt)	Activation of Angiotensin II , Catecholamine and Endotelin-1
No fibrosis	MAPK and Calcineurin pathway
Normal gene expression	Fibrosis, myocyte necrosis and apoptosis
Proportional chamber enlargement	Cardiac dysfunction

The table summarizes the differences in the cellular and molecular pattern between physiological and pathological hypertrophy. VEGF: Vascular endothelial growth factor; IGF-1: Insulin like growth factor; PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinase.



**Figure 1** The figure shows the Laplace relationship: The pressure (P) generated in a sphere is directly proportional to the wall tension (T) and inversely related to the radius of the sphere (r).

athletes<sup>[18]</sup>. These are specific markers of myocyte injury and strain, but do not indicate a permanent injury. Potential mechanisms have been showed to elucidate cTn elevation after intense exercise, but actually, the elevation of cTn levels in healthy individuals cannot be explained by any of these theories<sup>[18]</sup>. It is possible that exercise induces an increase in myocardial sarcolemma permeability, due to mechanical stress on the cardiomyocytes and to increased production of oxidative radicals or altered acid base balance exercise, with passive diffusion of cTn from the intra- to extra-cellular compartment<sup>[18]</sup>. Cellular stretching might cause transient disruption of the myocardial plasma membrane and then, the release of cTn<sup>[19]</sup>. Furthermore, it can stimulate integrins, mediating the transport of entire cTn molecules out of viable cardiomyocytes<sup>[20]</sup>. Increased levels of cTn are more common in cycling or triathlon and depend on the exercise intensity<sup>[21]</sup>.

Case reports have shown myocardial fibrosis and late gadolinium enhancement, associated with cTn elevation post-exercise, in a small number of veteran athletes, but the pathogenesis of these cases remains unclear<sup>[18]</sup>.

## EXERCISE-INDUCED MYOCARDIAL FIBROSIS

Despite the widely recognized benefits of regular physical

activity, high-level exercise training may be associated with increased arrhythmia risk and even with sudden cardiac death<sup>[22]</sup>.

The athlete's heart is a benign condition, representing a normal adaptation to chronic exercise, in which loss of myocytes and abnormal deposition of collagen do not usually occur<sup>[15]</sup>. Pathological hypertrophy is associated with apoptosis and necrosis; in this case, the loss of myocytes is replaced with excessive collagen deposition. Excessive collagen deposition increases the stiffness of the ventricles, with consequent impaired contraction and relaxation, electrical conduction system fibrosis and reduced capillary density, leading to myocardial ischemia and the transition from hypertrophy to failure<sup>[15]</sup>. Interestingly, recent studies have shown myocardial inflammation and fibrosis in animal models of long term, intensive exercise. Chen *et al*<sup>[23]</sup> forced rats to swim strenuously and found histological evidence of localized myocyte damage, myocardial necrosis and inflammatory infiltrates. Benito *et al*<sup>[24]</sup> instituted an intensive treadmill running protocol in rats and demonstrated an increase in atrial and ventricular inflammation and fibrosis and a greater risk of ventricular arrhythmias in the "marathon rats". Fibrosis and inflammatory infiltrates have been identified in well-trained athletes who underwent cardiac biopsy for high probability of identifying a cardiac pathology<sup>[25]</sup>. Histology offers the tangible evidence of fibrosis, but inflammatory infiltrates and fibrosis are

non-specific and their etiology can be supposed only by other clinical factors. Furthermore, cardiac biopsy is an invasive procedure with significant risks and it is not applicable in the absence of high suspicion of heart disease. An accurate, non-invasive surrogate tool for detecting fibrosis is cardiac magnetic resonance (CMR) imaging with gadolinium contrast. Gadolinium-based extracellular paramagnetic contrast agents concentrate in areas of fibrosis and thus can be used to characterize injured myocardium. Using gradient-echo inversion recovery imaging, fibrosis appears as bright signal, with a prolonged wash-out time for gadolinium [delayed gadolinium enhancement (DGE)], contrasting with the normal myocardium, which looks black<sup>[6]</sup>. Several studies have identified the presence of DGE in the heart of extensively trained veteran athletes. In most cases, the patches of DGE were very small and sited in the septum and in RV insertion points, regions subjected to local stretching during exercise<sup>[6]</sup>. More recently, La Gerche *et al.*<sup>[4]</sup> have shown myocardial fibrosis by CMR and a reduction in RV systolic function in athletes with long-term exercise, suggesting that the heart has a limited capacity to tolerate the overload exercise. The patches of cardiac fibrosis may be the substrate for ventricular tachycardia and sudden death, in predisposed individuals<sup>[4]</sup>. Some authors have recently suggested a new entity, the so called Phidippides cardiomyopathy: Long term strenuous exercise can induce cardiac dilation and also activates resident macrophages, pericytes, and fibroblasts, resulting in the deposition of collagen and fibrosis<sup>[26,27]</sup>. CMR can also specifically detect intra-myocardial fibrofatty infiltration of the RV wall, typical of the arrhythmogenic right ventricular cardiomyopathy (ARVC), which often leads to ventricular arrhythmias and usually appears in young adulthood and affected asymptomatic or minimally symptomatic individuals<sup>[27]</sup>. In conclusion, it is possible that the RV is more susceptible to fatigue than the left ventricle after prolonged exercise. It needs more studies to identify a probable effect of exercise "dose" and their implication in the development of heart failure.

## IS CARDIAC REMODELING IN ATHLETES ALWAYS BENIGN?

Cardiac adaptations to exercise not involve only the left ventricle, but all the heart chambers. Often these changes are absolutely physiological, but in some cases, they can predispose to pathological conditions, such as arrhythmias. Below, we report the main morpho-functional changes of the different cardiac structures in athletes and their implications in the pathogenesis of cardiovascular diseases.

## ATHLETE'S ATRIA FUNCTION AND DYSFUNCTION

Atrial abnormalities can be present in athletes, such as

a mild increase in atrial volume and diameter, and may be considered a physiological adaptation to exercise<sup>[28]</sup>. The pathophysiological mechanisms are not well defined. Studies in animal models have shown that, in rats, prolonged and vigorous exercise resulted in eccentric hypertrophy and diastolic dysfunction with atrial dilatation and fibrosis, especially in the atria and the right ventricle, and increased fibrotic mRNA compared with controls<sup>[24]</sup>. A recent meta-analysis of 7189 adult elite athletes have shown that exercise causes an increase in left atrium (LA) dimensions, compared with controls, evaluating both diameter and volume, corrected for body surface area. The endurance athletes reported the largest average LA diameters<sup>[29]</sup>. Since pre-adolescence, the long-term endurance exercise results in considerable bi-atrial remodeling and enlargement compared with sedentary subjects of the same age, with a preserved cardiac function<sup>[30,31]</sup>. LA enlargement could be considered part of athlete's heart, considering that the LA pressure rises during ventricular diastole more than in sedentary subjects, to maintain adequate filling whereas LV stiffness or pressure are increased<sup>[32]</sup>. On the other hand, there is evidence that the endurance exercise increases the risk of developing atrial fibrillation (AF) and atrial flutter in the middle age, in subjects without any clinical or echocardiographic signs of cardio-pulmonary pathologies or hypertension<sup>[33]</sup>. The mechanisms responsible for these arrhythmias might be: The major incidence of atrial ectopic beats in this population, as a consequence of physical activity; the influence of autonomic nervous systems, and in particular the vagal system, responsible for the "vagal AF"<sup>[34]</sup>; the atria dilatation, fibrosis, and inflammation induced by high exercise training and the atrial remodeling<sup>[33]</sup> (Table 2). In mice, exercise can induce TNF $\alpha$ -dependent activation of both NF- $\kappa$ B and p38MAPK, increasing inflammation and AF susceptibility<sup>[35]</sup>.

Moreover, AF might be closely connected with oxidative cellular changes and redox imbalance in the atrium. The oxidative species, generated from cardiomyocytes in stress conditions such as strenuous exercise, can increase inflammation and activate downstream molecular pathways, promoting morphological and electrical modeling. Recently, Mont *et al.*<sup>[36]</sup> have shown that loss of Nrf2, a gene with antioxidant function in the atria, could be associated with atrial hypertrophy and AF, suggesting that the preservation of the redox state is essential for the atrium health.

Finally, in athletes AF appears as some symptomatic and paroxysmal episodes that could become more frequent and progress to persistent AF. The GIRAFA study has showed that the crisis appears in the night or after the meal, related to an increased vagal tone<sup>[36]</sup>.

Data about right atrial (RA) function in top level athletes are lacking. Previously, our group has delineated the upper limits of RV and RA dimensions in highly-trained athletes and showed that right heart dimensions were greater in elite endurance-trained athletes than in age- and ex-matched strength athletes and controls<sup>[37]</sup>. Then, D'Ascenzi *et al.*<sup>[38]</sup> investigated the RA function and dimension in 100



**Table 2 Pathological mechanisms of atrial fibrillation in long-term athletes**

Pathological mechanism
Atrial ectopic beats
Vagal nervous system
Atrial fibrosis
Atrial dilatation
Myocardial injury
Inflammation
Redox imbalance

The table shows the most important mechanisms involved in atrial fibrillation exercise related.

top level athletes by standard echocardiography and 2D speckle tracking echocardiography and showed that RA area, volume, volume index, and inferior vena cava were significantly greater in athletes than in controls and the peak atrial longitudinal strain and peak atrial contraction strain values were lower in athletes than in controls. This strain reduction should not represent a real dysfunction, but only a physiological phenomenon, and can be included in the "athlete's heart"<sup>[38]</sup>.

## LV CHANGES IN EXERCISE RELATED AND PATHOLOGICAL CONDITIONS

In some highly-trained athletes, the LV wall thickness may be increased, mimicking a hypertrophic cardiomyopathy (HCM). The thickening is usually mild, but in some cases, it may be significant and creates difficulties to differentiate athlete's heart and hypertrophic cardiomyopathy, especially in the ambiguous "gray zone", when the wall thickness is of 13 to 15 mm (12 to 13 mm in women)<sup>[39]</sup>. This differential diagnosis is important, since most cases of sudden death in athletes are probably due to HCM<sup>[40]</sup>. Echocardiography plays an important role in the differential diagnosis: HCM is probable with LV end-diastolic cavity < 45 mm, evidence of pathogenic sarcomere mutation, family history of HCM, abnormal LV diastolic function, left atrial dilatation, and late gadolinium enhancement on contrast-enhanced CMR imaging. Usually athlete's heart is characterized by LV cavity enlargement (> 55 mm), peak VO<sub>2</sub> > 110% of expected, and thickness or mass decreases with short periods of detraining<sup>[41,42]</sup>. Pelliccia *et al.*<sup>[43]</sup> have shown that LV wall thickness ≥ 13 mm is mostly present in elite rowers and cyclists, and the upper limit appeared to be 16 mm (Figure 2).

Other conditions that can cause cardiac hypertrophy include valve disease, hypertension and non-compaction myocardium. Despite the prevalence of hypertension is approximately 50% lower in athletes compared with the general population, it is also the most common cardiovascular condition in athletes. The pharmacological therapy can be difficult for the competition regulations and potential adverse effects<sup>[44]</sup>. It is important to

diagnose this condition, because it is associated with an increased risk of developing heart failure. Recently, an elevated prevalence of LV noncompaction (LVNC) has been reported in athletes, phenotypically characterized by a more thick endocardial noncompact layer, increased trabeculations and deep recesses<sup>[45]</sup>. Caselli *et al.*<sup>[46]</sup>, in a recent study, have shown that in a large population of athletes, only a small subgroup presented LVNC. The increased trabeculations may represent a LV variant of athlete's heart without any clinical significance<sup>[46]</sup>.

Figure 3 summarizes the different characteristics of physiological remodeling and pathological condition of LV.

## EXERCISE-RELATED RIGHT VENTRICLE REMODELING

Strenuous and prolonged exercise can cause RV dysfunction, usually transient, with evidence of increased biomarkers of cardiac damage. On the other hand, repeated bouts of exercise can lead to RV structural remodeling and arrhythmias and can lead to a syndrome similar to familial ARVC, without an identifiable genetic predisposition<sup>[47,48]</sup>. ARVC is present in 4% to 22% of athletes with sudden cardiac death<sup>[49,50]</sup>. As mentioned above, the RV function may be more interested by intense endurance training, therefore the diagnostic criteria for ARVC should be nonspecific in athletes with electrocardiographic anomalies and biventricular dilation.

Marcus *et al.*<sup>[51]</sup> in a multi-center study of 108 probands with ARVD/C showed that 34% were athletes. Vigorous or long term athletic exercise might facilitate the phenotypic expression of ARVC due to the repetitive stretch of the RV with an underlying genetic desmosomal protein anomaly<sup>[51]</sup>.

Signs of RV dysfunction seem to include: Syncope; Q waves in precordial leads; augmented QRS duration; three abnormal signal averaged electrocardiography parameters; delayed gadolinium enhancement; RV ejection fraction < 45% or wall motion anomalies at CMRI; > 1000 ventricular extra-systoles (or > 500 non-RV outflow tract) per 24 h; ventricular tachyarrhythmia or abnormal blood pressure response during exercise (Table 3)<sup>[52,53]</sup>. RV cavity size is not significantly larger in ARVC patients compared with athletes, whereas RV outflow tract is larger in ARVC subjects than in athletes<sup>[53]</sup>. The thickened and high reflective moderator band, commonly considered typical of ARVC, are present also in athletes and could be due to RV dilatation<sup>[53]</sup> (Figure 4). Further studies regarding the differential diagnosis between ARVC and physiological remodeling in athletes are needed to create useful clinical diagnostic algorithms.

## PERFORMANCE-ENHANCING DRUGS AND CARDIAC DAMAGE

Some banned athletic performance-enhancing drugs

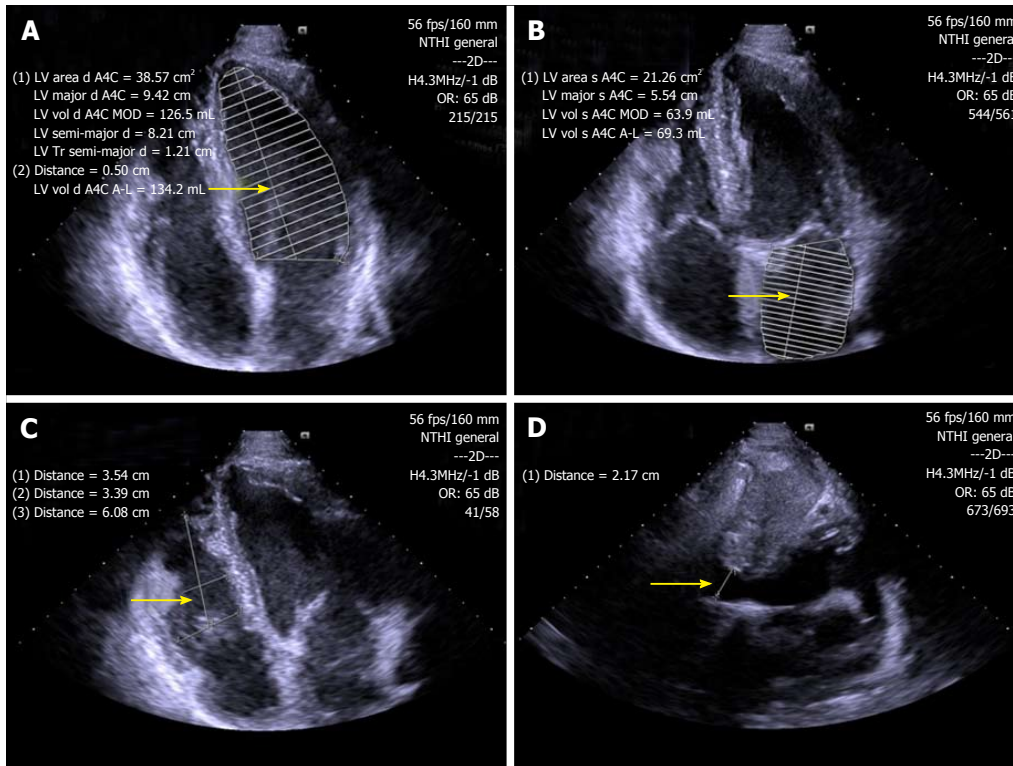


Figure 2 Standard B-mode echocardiography of endurance athlete showing enlargement of left ventricular (A), left atrial (B) and right ventricular (C) chambers, as well as inferior vena cava vein dilatation (D) (arrows). LV: Left ventricular.

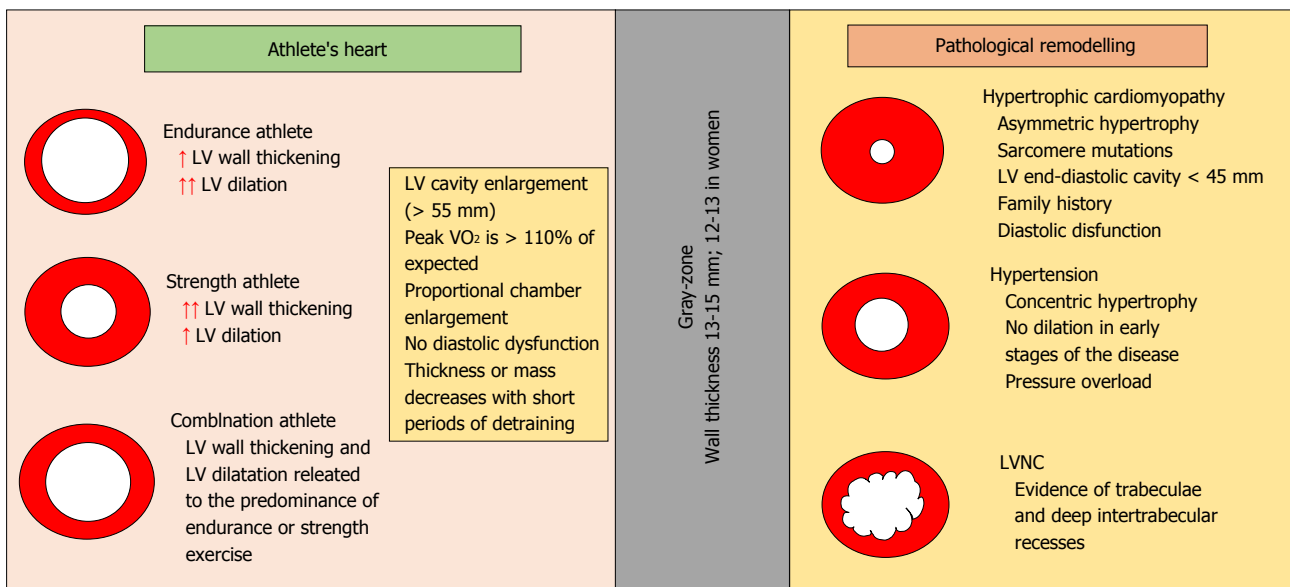


Figure 3 Different characteristics of physiological remodeling and pathological condition of the left ventricle. LV: Left ventricular; LVNC: LV noncompaction.

might have cardiac toxic effects, such as anabolic-androgenic steroids (AASs) and growth hormone (GH).

Healthy athletes abusing AASs may exhibit LV hypertrophy with both systolic and diastolic myocardial dysfunction and focal areas of DGE at CMR, with non-ischemic distribution<sup>[54]</sup> (Figure 5). AASs have direct toxicity on myocardial structures, with increased collagen deposition, fibrosis, and intimal hyperplasia of the intra-

mural coronary vessels with chronic ischemic damage and microcirculation alterations. Moreover, testosterone might inhibit the extra-neuronal uptake of neuroamine and consequently result in vasospasm due to an abnormal vascular response to norepinephrine<sup>[55]</sup>. Post-mortem studies of athletes who used AASs have found infiltration of eosinophils into myocardial cells, as well as destruction of myofibrils. Endothelial dysfunction was

**Table 3** Indicators of right ventricle pathology

Episodes of syncope
> 1000 ventricular extra-systoles (or > 500 non-RV outflow tract) per 24 h; ventricular tachyarrhythmias; Q waves in precordial leads; augmented QRS duration
≥ 3 abnormal signal averaged electrocardiography parameters
Delayed gadolinium enhancement; RV ejection fraction < 45%, or wall motion abnormalities at CMRI; impaired RV strain imaging
Attenuated blood pressure response during exercise
Dilatation of RV outflow tract

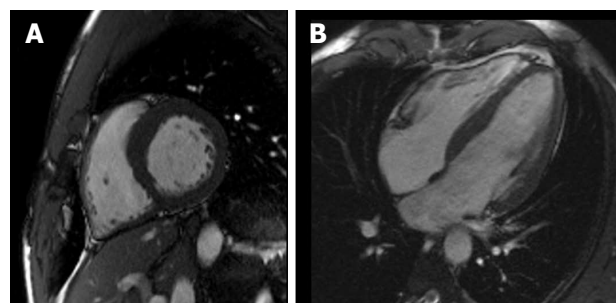
The table shows the indicators of right ventricle pathology (ARVC *vs* athlete's heart). CMRI: Cardiac magnetic resonance imaging; RV: Right ventricle; ARVC: Arrhythmogenic right ventricular cardiomyopathy.

also observed<sup>[56]</sup>.

GH abuse has tainted many sports, including baseball, cycling, and track and field, for promoting an increase in muscle mass, though its effects on physical performance are not completely supported by the literature<sup>[57]</sup>. GH promotes cellular growth by stimulating protein synthesis, inhibiting catabolism, and inducing IGF-1 production. At the molecular level, GH binds its receptor and induces subsequent expression of growth-promoting molecules<sup>[58]</sup>. GH, both in excess or in deficient states, is related to increased cardiovascular mortality. The excess, like in acromegaly or in doping, results in cardiac hypertrophy and an increase in collagen, fibrosis, and cellular infiltration. *In vivo* studies on healthy mice demonstrated that increased GH levels induce significant LV hypertrophy and an increase in concentric anterior and posterior wall thicknesses, LV diastolic diameters and volumes, and cardiac output<sup>[59]</sup>. Unfortunately, the majority of conclusions about GH abuse and its cardiac effects result from data regarding acromegaly and not from direct data, which are lacking.

Also, erythropoietin (EPO), which increases hematocrit levels and thus improves aerobics capacity, may lead to cardiac dysfunction, increasing blood viscosity and cardiac afterload, and predisposes to hypertension and thromboembolism. Experimental studies have shown hypertension, cardiac hypertrophy and fibrosis after administration of high doses of EPO<sup>[60]</sup>.

Thyroxine is used, generally, by athletes to promote weight loss. Thyroid hormones (TH) play an important role in cardiac growth and might cause cardiac hypertrophy and also heart failure if they are in excess. High levels of TH might result in elevated heart rate, decreased total peripheral resistance, widened pulse pressure, blood volume expansion, increased LVM and cardiac output, with improved contractile function and hemodynamic parameters in the short term. Long-standing hyperthyroidism can lead to dilatation of cardiac chambers and heart failure. Interestingly, the diminished cardiac function is often reversible when euthyroidism is re-established<sup>[61]</sup>. Weltman *et al*<sup>[61]</sup> showed that hyperthyroid rodents had important cardiac hypertrophy and adverse cardiac remodeling with chamber dilatation, LV systolic and diastolic dysfunction, decreased relative



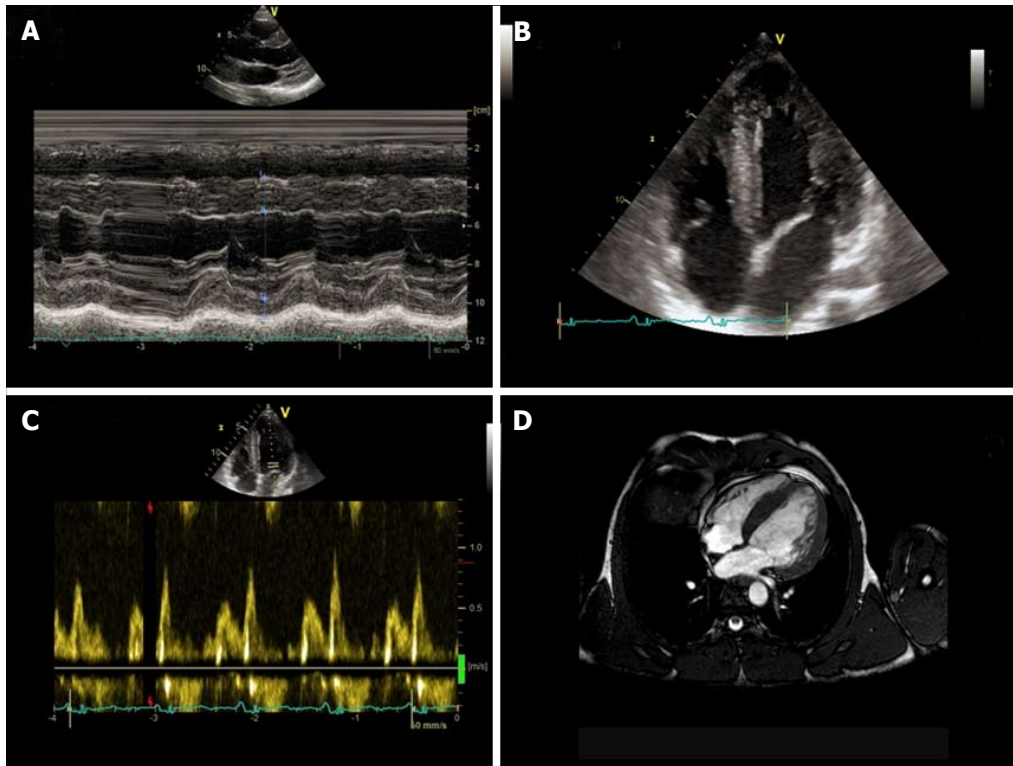
**Figure 4** Cardiac magnetic resonance depicting in short-axis (A) and long-axis (B) view balanced biventricular enlargement in endurance athlete.

wall thickness, and fibrosis<sup>[61]</sup>. Few data in the literature are about the cardiac consequences of the prolonged use of thyroxine treatment. Thyroxine treatment, in high doses which suppress serum thyrotropin to below normal, has been associated with LV hypertrophy (in the absence of significant changes in heart rate, stroke volume, blood pressure, and LV systolic function), but untreated thyrotoxicosis resulted in more pronounced cardiovascular changes than thyroxine treatment<sup>[62]</sup>. Further studies are necessary to evaluate the cardiovascular risk in patients treated with thyroxine.

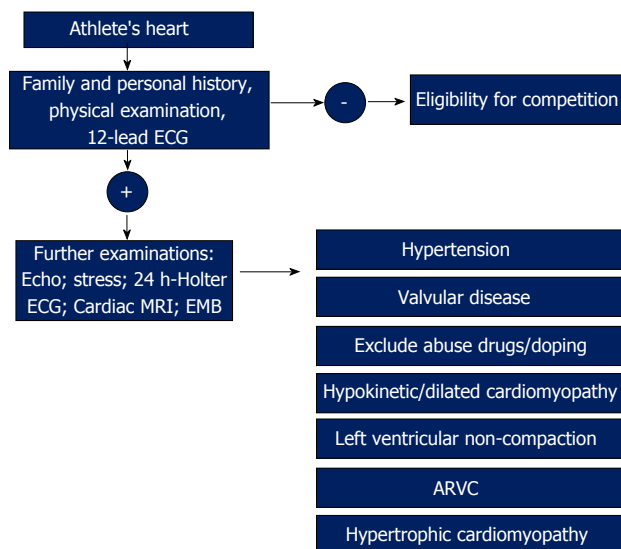
Many other drugs are responsible for heart failure in athletes, such as corticotrophin, beta 2 agonists, amphetamines and cocaine. Often athletes use combinations of different banned drugs, resulting in additive effects on cardiac remodeling. Cardiac alterations may lead to arrhythmias, heart failure and sudden death. It is important to exclude the abuse of these drugs, when athletes with heart dysfunction come to our attention. Figure 6 shows a flow chart to differentiate athlete's heart from pathological conditions.

## ENERGY DRINK CONSUMPTION AND HEMODYNAMIC EFFECTS

A growing number of case reports of cardiovascular adverse events associated with energy drinks (EDs) are present in the literature. The use of EDs is more common in young students and in athletes. The consumption of EDs negatively affects the hemodynamic system. Important changes in arterial pressure and heart rate may occur with the ingestion of only one can (355 mL drink volume). Furthermore, it seems that EDs may diminish cerebral blood velocity, increasing breathing frequency<sup>[63]</sup>. Caffeine and sugar appear to be the ingredients underlying hemodynamic impact of EDs. Taurine and vitamin B complex play a minor role<sup>[64]</sup>. Genetic polymorphisms in cytochrome P-450 enzymes and variations of adenosine receptors play a role in the different responses to the caffeine<sup>[65]</sup>. Caffeine improves athletic performance in rowing<sup>[66]</sup>, swimming<sup>[67,68]</sup>, soccer<sup>[69]</sup> and hockey<sup>[70]</sup>. On the other hand, EDs can cause many cardiovascular adverse



**Figure 5 Non-invasive evaluation of power athlete abusing of steroids.** Standard M-mode (A) and 4-chamber view B-mode (B) echocardiography, evidencing severe left ventricular hypertrophy, with diastolic dysfunction (C) underlined by Doppler transmitral flow pattern. Cardiac magnetic resonance confirmed severe left ventricular hypertrophy (D).



**Figure 6 The management of athlete's heart.** The figure shows an algorithm to distinguish athlete's heart from pathological conditions. ARVC: Arrhythmogenic right ventricular cardiomyopathy; ECG: Electrocardiograph; MRI: Magnetic resonance imaging.

effects (Table 4), such as hypertension, palpitations, ischemic stroke, epileptic seizure<sup>[71]</sup> and myocardial ischemia, with no additional trigger<sup>[72]</sup>. The possible mechanism is related to the caffeine interaction with the G-protein coupled receptors on the cardiomyocytes that leads to an increase in intracellular cyclic-AMP and calcium concentrations with chronotropic and inotropic

**Table 4 Adverse effects of energy drinks**

Adverse effect
Hypertension
Palpitations/arrhythmias (atrial fibrillation)
QTc prolongation
Myocardial ischemia
Ischemic stroke/Transient ischemic attack
Epileptic seizure
Anxiety, insomnia, irritability
Psychosis/Mania

The table shows the most common adverse effect of consumption of energy drinks.

effects<sup>[73]</sup>. Large studies regarding EDs and their effects on the cardiovascular system are necessary, especially for the widespread consumption of these substances in recent years.

## CONCLUSION

The exact clinical significance and prognostic value of cardiac injury and fibrosis in athletes are unknown. Physiological remodeling is characterized by specific molecular activation and gene expression. More large studies are needed to gain a better understanding of these conditions and the pathological changes in the heart structure in athletes and to investigate the cardiac effects of performing-enhanced drugs and EDs in this population.



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