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CARDIAC RADIOLOGY

Advanced cardiac imaging in athlete's heart: unravelling the grey zone between physiologic adaptation and pathology

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Abstract

Over the last decades, interest toward athlete's heart has progressively increased, leading to improve the knowledge on exercise-induced heart modifications. Sport may act as a trigger for life-threatening arrhythmias in patients with structural or electrical abnormalities, hence requiring to improve the diagnostic capability to differentiate physiological from pathological remodeling. Pathological alterations are often subtle at the initial stages; therefore, the challenge is to promptly identify athletes at risk of sudden cardiac death during the pre-participation screening protocols. Advanced imaging modalities such as coronary computed tomography angiography (CCTA) and cardiac magnetic resonance (CMR) can non-invasively depict coronary vessels and provide a deep morpho-functional and structural characterization of the myocardium, in order to rule out pathological life threatening alterations, which may overlap with athletes' heart remodeling. The purpose of the present narrative review is to provide an overview of most frequent diagnostic challenges, defining the boundaries between athlete's heart remodeling and pathological structural alteration with a focus on the role and importance of CCTA and CMR.

Keywords Athlete's heart · Sudden cardiac death · Cardiac magnetic resonance · Cardiac computed tomography · Cardiomyopathy

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Sudden cardiac death: epidemiology and etiology

Sudden cardiac death (SCD) prevention in athletes is a public health concern. Sudden cardiac death is defined as a non-traumatic, unexpected death occurring within one hour from the onset of symptoms in an apparently healthy individual [1]. It is a rare but devastating occurrence usually affecting young and apparently healthy individuals, with an extensive social impact due to the preventable nature of this event. The reported incidence of SCD in young athletes is quite variable ranging from 0.6/100,000 [2] to approximately 3.6/100,000 athletes per year [3], involving mainly males and Afro-Americans. The incidence in athletes is from 2.5 [4] to 4.5-fold higher [5] than in age-matched non-athletic young population, suggesting the role of sport as a trigger for SCD.

The aetiology of SCD varies with athletes' age. SCD in young athletes (< 35 years) is mostly due to inherited structural heart diseases, specifically to hypertrophic cardiomyopathy (HCM), which accounts for approximately one-third of deaths in US competitive athletes [2] and arrhythmogenic

right ventricular dysplasia/cardiomyopathy (ARVD/C), as the most common cause of athletic deaths in Veneto region of north-eastern Italy [3]. Reported differences may be related to different genetic and myocardial substrate and to systematic pre-participation screening in Italy for more than 30 years with prompt identification and disqualification of athletes affected by HCM [3].

The second most common cause of SCD in athletes is congenital coronary artery anomalies with origin from the "wrong" aortic sinus. The least common causes (5–8%) include myocarditis, valvular heart disease and ion-channel disorders [6].

In master athletes (> 35 years), the 80% of SCD is due to atherosclerotic coronary artery disease (CAD) [5].

Pre-participation screening (PPS) protocols are essential to identify subtle heart diseases, reducing the risk of SCD; however, they differ among countries. Differently from the US, where the inclusion of ECG in PPS is still controversial, ECG has been extensively integrated in PPS for more than ten years in Europe, due to its high sensitivity [7]. However, some cardiac conditions such as coronary anomalies, cardiomyopathies (e.g. HCM/ARVC) and premature CAD cannot be early identified on ECG [2].

Echocardiography is a valid and complementary diagnostic tool, which allows a morpho-functional evaluation of the heart, distinguishes physiological from pathological ventricle hypertrophy and identifies regional wall motion abnormalities [6].

The value of advanced cardiac imaging is established in current guidelines [8, 9]. In fact, for inconclusive echocardiography or in suspected cases of coronary abnormalities or cardiomyopathies, coronary computed tomography angiography (CCTA) and cardiac magnetic resonance (CMR) are indicated [8, 10]. In particular, CCTA has the advantage to depict abnormal coronary vessels anatomy in young athletes and atherosclerotic involvement in master athletes, non-invasively and with limited radiation exposure, while CMR is indicated for the discrimination of normal adaptation to cardiomyopathy and for risk stratification [8] due to its capability to accurately characterize myocardial volumetry, mass, contractility and wall motion alteration, with the undisputed advantage of structural and microstructural characterization. Moreover, CMR can identify inherited cardiac disease, acute and chronic damages from different aetiologies [11] and also provides prognostic information.

The Athlete's heart: physiology and adaptive mechanisms

Athlete's heart is structurally and physiologically different compared to general population.

During exercise there is an increase in oxygen consumption (VO2) and biventricular cardiac output, associated to decrease in vascular resistance, which is less in the pulmonary circulation. This mismatch between increased flow and vasodilation results in an abnormal increase in pulmonary artery pressure and right ventricle (RV) afterload, with a significant rise in RV workload.

Hemodynamic and cardiac adaptations differ according to the type and intensity of exercise (endurance or strength exercise). Regular athletic training determines a complex of structural, functional and electrical myocardial remodeling (Fig. 1).

Since first echocardiographic studies in 1975, athletes were shown to develop left ventricle hypertrophy (LVH) predominantly eccentric in endurance athletes and more frequently concentric in strength athletes. Compared to general population, athletes show a 15–20% greater left ventricle wall thickness (LVWT) and 10–15% greater LV size. These changes are adaptive mechanisms, which can regress in case of detraining. Notably, LVWT > 13 mm and LV diameter > 60 mm are rare in healthy athletes [12, 13].

Left Atrium (LA) dilation is the second structural adaptation in trained athletes, mainly in endurance sports. Increased LA size (cut-off value: 46 mm in females; 50 mm in males) can be explained by concomitant LV cavity enlargement and volume overload [14], which explains the higher incidence of supraventricular arrhythmias encountered in adult athletes [15].

Right Ventricle (RV) is considered the Achille's Heel of athlete adaptation mechanism. At rest when cardiac flow is low, there are modest atrio-ventricular pressure gradients. During exercise, the high-flow state results in substantial atrial filling and pressure rise during systole when the atrioventricular valves are closed. This high LA pressure backs up, through the pulmonary circulation and result in RV afterload elevation. The higher RV afterload is the determinant of RV dilation.

Because of pericardial constraint, the increase in RV volumes causes septal shift toward the left ventricle in early diastole that can attenuate early diastolic filling of the LV and further increase in LA pressure. Thus, the increase in RV afterload becomes a critical constraint during high intensity exercise in healthy subjects [16].

Regarding functional adaptation, elite athletes appear to have a higher capacity to increase stroke volume during exercise [17]. In particular, endurance athletes have greater effective LV diastolic chamber compliance and distensibility than non-athletes and thus have a steeper slope of their Starling curve, which relates LV filling pressure to stroke volume.

Despite exposure to vigorous training, no increase in cardiovascular events or deterioration in global left ventricle systolic function or wall motion abnormalities incidence has

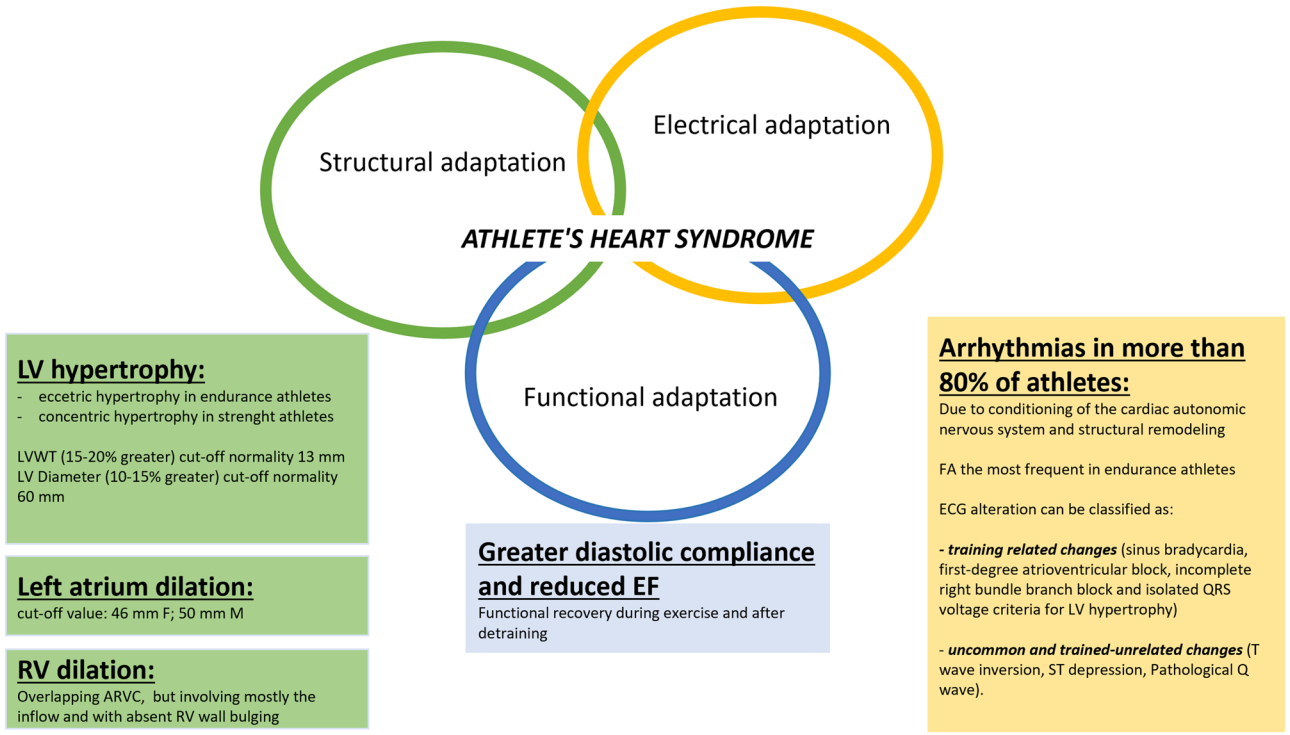

Fig. 1 Structural, functional, and electrical myocardial remodeling induced by exercise training in competitive athletes

been evident. Only a transient reduction in LVEF has been demonstrated after prolonged strenuous exercise, which is termed "cardiac fatigue" [18].

During exercise, the increased LV cardiac output determines an augmented venous return to right chambers, with consequent progressive enlargement. This is associated to an increase in wall thickness and altered diastolic function for increased atrial component of the flow pattern across tricuspid valve. Intense endurance exercise causes acute RV dysfunction that recovers in the short term after detraining. However, chronic structural changes and reduced right ventricle function are evident in some athletes. In addition, global and regional right ventricle systolic function at rest are mildly reduced in endurance athletes compared with non-athletic control subjects. These findings can be considered as "physiological" adaptation to intensive exercise [19].

More than 80% of competitive athletes manifest changes in resting ECG reflecting physiological adaptation to training; changes potentially confounded with cardiovascular pathology occur in 10–14% of ECG. Electrical adaptations in athletes result from conditioning of the cardiac autonomic nervous system (increased vagal tone and/or sympathetic withdrawal) and structural remodeling. Increased vagal tone is responsible for findings such as bradycardia, sinus arrhythmia, early repolarization and first-degree Mobitz type I AV block. Therefore, ECG findings can be classified [20] into: training related changes (sinus bradycardia, first-degree atrioventricular block, incomplete right bundle branch block and isolated QRS voltage criteria for LV hypertrophy) and uncommon and trained-unrelated changes (T wave inversion, ST depression, Pathological Q wave). Structural, functional and electrical changes in the athlete's heart must be always related to other factors such as age, sex and ethnicity.

In fact, women exhibit adaptive mechanisms analogous to men, but in absolute terms with less quantitative effects and therefore show analogous electrical remodeling but lower prevalence of LVH. Indeed, LVWT > 11 mm in the Caucasian woman and > 13 mm in the African Caribbean woman is rare [21]. African/Afro-Caribbean athletes exhibit marked repolarization anomalies and more significant LVH.

Performance-enhancing drugs may facilitate exercise capacity and increase athletic cardiac remodeling; however, the health consequences are still extensively unknown. Abergel et al. [22] demonstrated that cyclists in the 1999 Tour De France had larger LV diameter and lower systolic function than cyclists in 1995. One potential explanation is that erythropoietin use is believed to have increased dramatically over this period.

Hypertrophic phenotype and HCM

The type of sport practiced with age, sex, ethnicity, genetics lead to different severity of cardiac hypertrophic remodeling, which can be identified with echocardiography and better characterized with CMR. The majority of athletes exhibit normal LV geometry; however, a concentric hypertrophy usually symmetrical that does not exceed 16 mm (Fig. 2) is reported in up to 10% of white athletes and up to 18% of black athletes [23].

Importantly, athletes with HCM have a lower degree of hypertrophy than sedentary patients with HCM, however, in most of them (> 85%) the hypertrophy is asymmetric with LVWT > 16 mm [24].

Although distinguishing definitive pathological hypertrophy from a normal myocardium could be relatively easy, a certain number of athletes show intermediate features (e.g. LVWT between 13–15 mm in males and 12–15 mm in females), which causes a challenge to make a definitive diagnosis. Therefore, how to distinguishing hypertrophic athletes' heart remodeling from HCM?

Hypertrophic cardiomyopathy is the most common genetic cardiac disorder, representing the first cause of sudden cardiac death among athletes. It is a heterogeneous entity with a variable clinical presentation. Fibers disarray, interstitial fibrosis and arteriolar thickening are the pathological characteristics that lead to adverse remodeling, arrhythmias, ischemic homologues and sudden cardiac death.

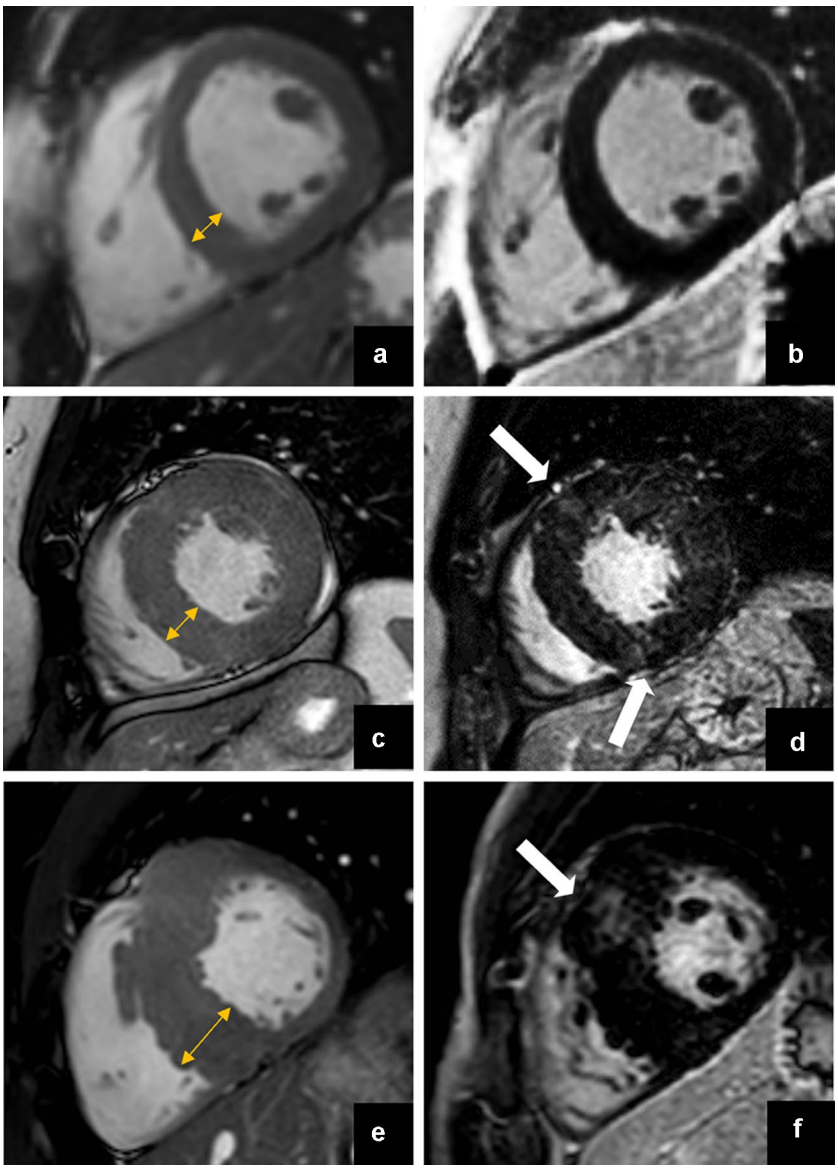

Fig. 2 Cardiac Magnetic Resonance in hypertrophic adaptation in athletes (on top) and hypertrophic cardiomyopathy (on bottom). Hypertrophic adaptation in athletes is typically characterized by mild symmetric hypertrophy, rarely over 13 mm and never over 16 mm (14 mm orange arrow in **a**), with absence of late gadolinium enhancement (**b**). Differently, HCM is characterized by myocardial hypertrophy with maximal LV wall thickness greater than or equal to 15 mm in the end-diastolic phase (24 and 30 mm orange arrows in c and e, respectively), most frequently with an asymmetric involvement (**e**, **f**). Late gadolinium enhancement in HCM involves the ventricle walls with greater thickness, most frequently with patchy mid-wall distribution (white arrows in **d**, **e**). Rarely, HCM exhibits symmetric phenotype (**c**, **d**), the most difficult to differentiate from exercise induced hypertrophic adaptation

Phenotypically, HCM ranges from symmetric to asymmetric forms with septal, lateral or apical hypertrophy, while right ventricular involvement is relatively rare.

Less common forms may result in left ventricular non-compaction and transmural crypts [21]. There are different stages of the disease with different CMR findings and sudden cardiac risks. Initially HCM may be silent, with normal wall thickness, then it may evolve to classic form and eventually can present, in end stage phases, an adverse remodeling with restrictive pattern.

CMR plays a pivotal role in HCM diagnosis, phenotypization and prognostication, but also in the assessment of dynamic obstruction of the LV outflow tract, microvascular ischemia, myocardial fibrosis, cardio-embolic risk and for surgical planning.

Late gadolinium enhancement is frequent in patients with HCM (around 65% of cases) [25], while it is rare among young athletes (3–13%) [26] (Fig. 2).

Late Gadolinium Enhancement (LGE) typically involves hypertrophied LV walls and provides prognostic information. Chan [27] demonstrated that extensive LGE, defined as ≥ 15% of LV mass, was associated with > twofold increase in SCD risk in asymptomatic cases. The recent introduction of mapping technique has opened the scenario to the possibility to quantify the extracellular volume fraction (ECV). A few promising studies showed the possibility to distinguishing initial stage of HCM from physiological athletes adaptation by measuring the ECV. This is due to prevalent contribution of myocyte hypertrophy to the increase in LV mass in athletes, with subsequent relatively small ECV; differently from HCM in which the ECV is significantly enlarged also at initial stages [28, 29].

Furthermore, CMR is capable to exclude several other causes of left ventricular concentric hypertrophy, such as Anderson Fabry disease, aortic stenosis and amyloidosis [30].

Anderson-Fabry disease is a rare X-linked disorder with systemic involvement and different myocardial disease penetrance. CMR shows concentric hypertrophy, diastolic dysfunction and infero-lateral wall enhanced striae. Typically, in these patients native T1 mapping has low values (< 900 ms at 1.5 T), due to the high concentration of myocardial fat caused by the intracellular accumulation of glycosphingolipids [30].

Amyloidosis is a systemic disease, characterized by extracellular deposition of amyloid material. Because of widespread and substantial extracellular infiltration, ECV is markedly increased (> 45%) with higher values in respect to the other forms of cardiomyopathy, moreover CMR might demonstrates a transmural enhancement with a "Zebra pattern" [30, 31].

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC is a genetic cardiomyopathy in which the loss of desmosomal integrity leads to a fibrofatty replacement of myocardial tissue [32, 33] predisposing to ventricular arrhythmias, right ventricle enlargement and dysfunction (Fig. 3). Although the right ventricle is the most involved, biventricular and left-dominant variants exist [34] (Fig. 4).

Diagnosis is based on structural, functional, electrophysiological and histological abnormalities, included in the 2010 International Task Force (ITF) criteria [35].

Some studies have revealed that vigorous and long-term exercise may facilitate clinical manifestations of ARVC, increasing the risk of SCD [3, 36]. ARVC has been identified

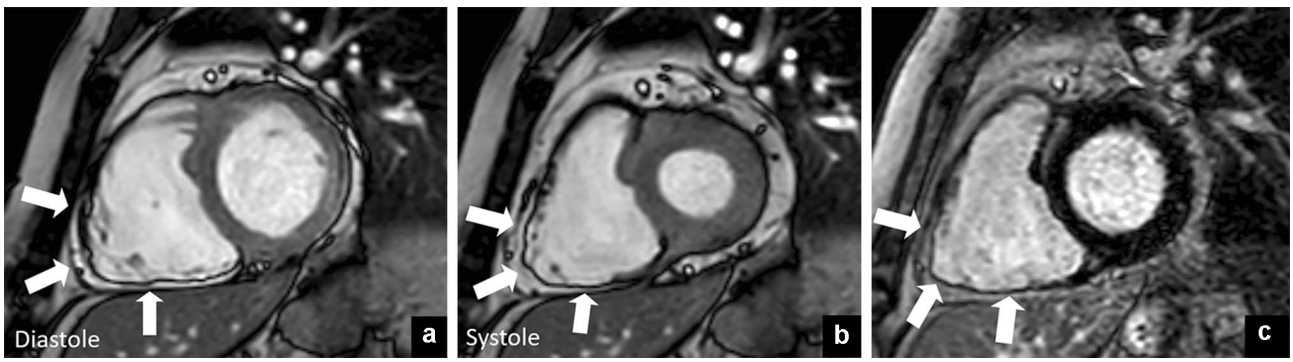

Fig. 3 CMR features in a 54-years-old woman affected by right arrhythmogenic ventricular cardiomyopathy. Cardiac Magnetic Resonance shows an enlarged right ventricle (EDV = 185 ml; EDV/BSA = 90 ml/mq) with impaired systolic function (EF = 37%). The right ventricular wall is thin and irregular (arrows in **a**) with systolic bulging (arrows in **b**) and increased trabeculation on the free and diaphragmatic wall. Late gadolinium enhancement short-axis image shows thin scars involving the free right ventricle wall (arrows in **c**). Left ventricle volume is in the range of normality (EDV/BSA = 64 ml/mq), with normal systolic function (67%), without segmental wall motion alteration

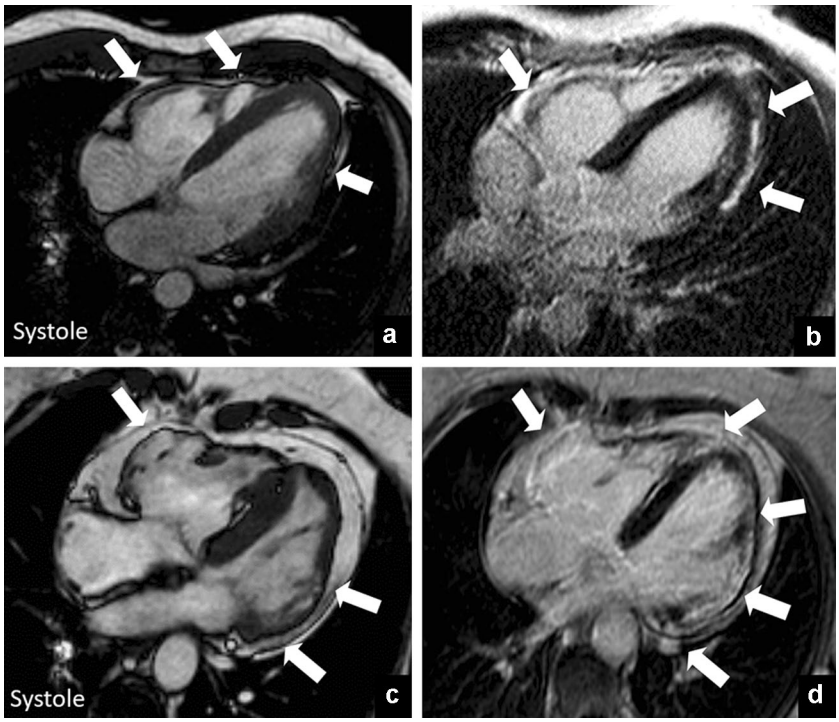

Fig. 4 Biventricular and left dominant arrhythmogenic cardiomyopathy. Cine and LGE images in genetic confirmed arrhythmogenic cardiomyopathy with biventricular (**a**, **b**) and left-dominant involvement (**c**, **d**). Cine images show enlarged ventricles, with wall motion alteration of free RV wall (hypokinesia in **a** and marked dyskinesia in **c**) and of lateral LV wall (arrows in a and c), with biventricular reduced EF (≤ 50% in both cases). Wall motion alterations associated to irregular wall thinning and marked biventricular fibrofatty replacement on LGE images (**b**, **d**), with extensive involvement of the LV in left-dominant arrhythmogenic cardiomyopathy (**d**)

in 4–22% of athletes with SCD [37]. Endurance athletes are over-represented among patients with ARVC, but the evidence of genetic or familial involvement is rare [38, 39] and differential diagnosis between familial cardiomyopathy from a long-term physiological remodeling due to prolonged exercise is challenging. In fact, training-induced RV modification often overlaps with ARVC major or minor criteria [40]. According to literature, RV dilation is frequent in athletes and often matches ARVC task force criteria (end diastolic volume indexed for body surface area ≥ 110 ml/m^2 in males or ≥ 100 ml/m^2 in females) [35, 41], often accompanied by a concomitant remodeling of LV, mostly involves the inflow tract in athletes' heart, whereas ARVC patients show both inflow and outflow tract dilation [42, 43]. Furthermore, bulging or aneurysms of RV lateral wall are not found in healthy athletes, while they are common findings in ARVC [44] (Table 1).

Even though tissue characterization of the RV is not included in the ITF Criteria, CMR, in particular LGE, provides useful information regarding RV myocardial tissue [45]. In endurance athletes, LGE is frequently found in the interventricular septum at the junction point with the free wall [19], whereas the most common localization of RV fibrosis in ARVC is the free lateral wall [46]. Differential diagnosis also includes the evaluation of clinical and electrocardiographic features: non-vasovagal syncope

Table 1 Main differences between athlete's heart and Arrhythmogenic Right Ventricle Cardiomyopathy (ARVC)

	Imaging features					Clinical feature	
	RV dilation	RV wall motion abnormalities	LV dilation	LGE	Symptoms	Family history of SCD or cardiomyopathy	ECG abnormalities
Physiological adaptation to exercise (athletes' heart)	RV chamber and inflow tract	–	+	Posterior RV insertion point (if present)	–	–	
ARVC	Both inflow and outflow tract	Bulging or aneurysms of RV free lateral wall	–	RV free lateral wall	Non-vasovagal syncope	+	T-wave inversion in V1-V4 and ST tract elevation/ Epsilon wave

ECG: electrocardiogram; RV: Right Ventricle; LV: Left Ventricle; LGE: Late Gadolinium Enhancement; SCD: Sudden Cardiac Death

[40] and depolarization abnormalities with T-wave inversion in V1-V4 and ST tract elevation [44]. Given that actual ITF criteria does not include cut-off values for athletes, the correct diagnosis is of fundamental importance to discriminate between ARVC, which can lead to SCD, from a benign adaptation of the RV to endurance exercise [47]. Apart from electrophysiological and clinical features, CMR represents an essential tool to detect both functional and morphological abnormalities in order to distinguish pathological from physiological RV and LV characteristics.

Dilated phenotype and dilated cardiomyopathy (DCM)

Endurance sport determines dilatation of the myocardial chambers due to long-term volume and pressure overload. This exercise-induced cardiac remodeling can overlap with dilated cardiomyopathy (DCM) in its initial stage, with mildly depressed ejection fraction (≤55%) and enlarged LV (LVEDD > 58 mm and LVEDV > 150 ml) (Fig. 5). DCM is defined as a dilated LV with reduced ejection fraction (EF) in the absence of significant ischemic heart disease, hypertension, or valvular pathology and is reported as a rare but possible cause of SCD in athletes [48].

Abergel et al. in 2004 [22] published a study conducted on 286 professional cyclists aimed to identify cut-off values for normal left ventricle adaptation in response to training. They identified cutoff values of 60 mm for end-diastolic left ventricular diameter (EDDLV) and 52% for left ventricular ejection fraction (LVEF). However, the limited data on CMR [49, 50] showed LV short-axis diameter > 60 mm in approximately 50% of elite male athletes, a condition rare in female athletes. Moreover, resting LVEF could be lower than normal in endurance athletes; Prakken et al. found 45–50% LVEF in 28% of athletes and 40–45% in 24% of athletes [49,

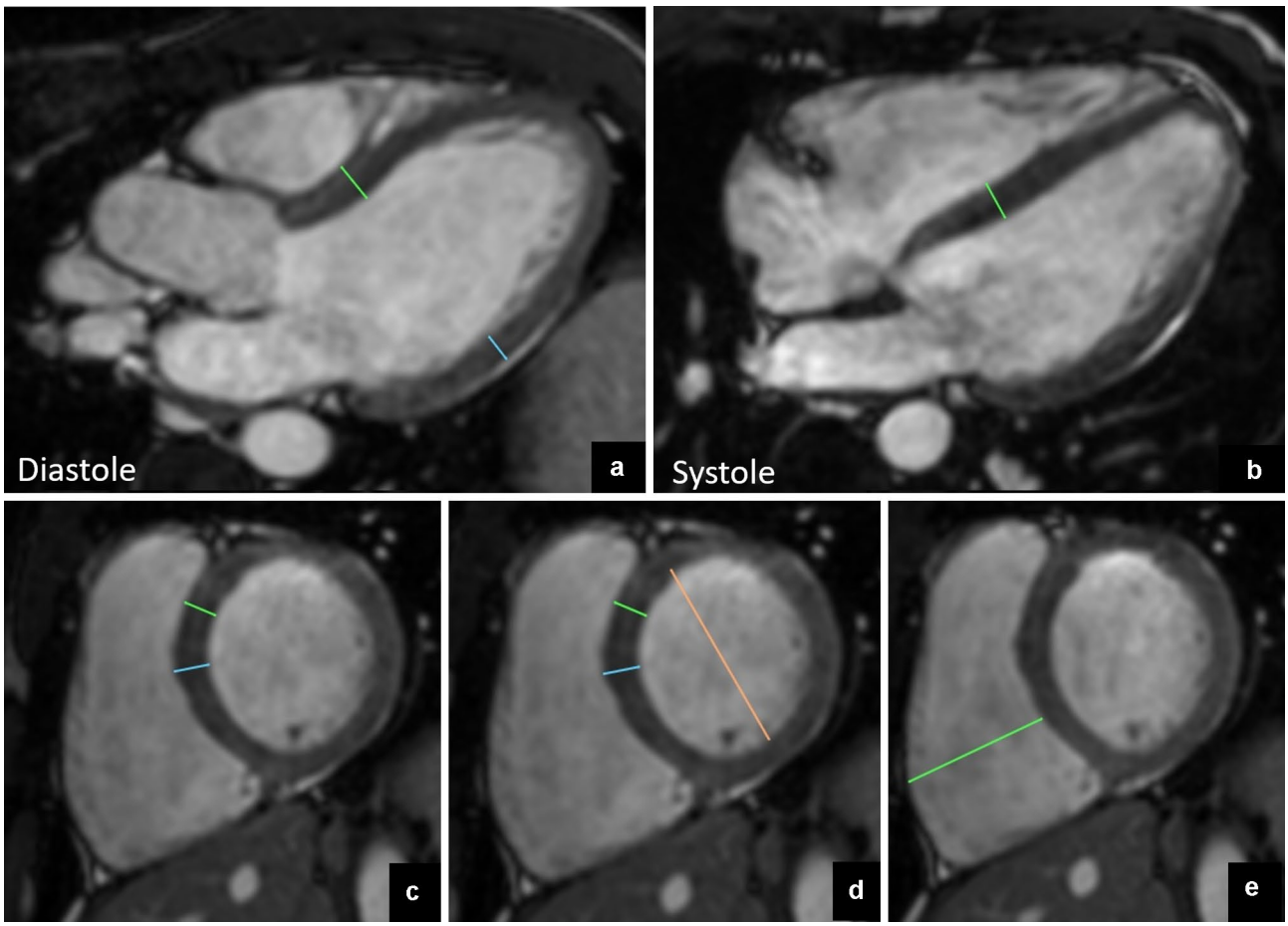

Fig. 5 Dilated phenotype in athletes' heart. Cine images show enlarged LV (**a**–**c**), with mildly reduced resting systolic function (EF = 50%). LV wall thickness is preserved (**a**, **c**), with a slightly increased apical trabeculation. RV volume and function are preserved. The grey zone of dilated adaptation to training is defined by LV enlargement (LVEDD > 58 mm or LVEDV > 150 mL) with borderline ejection fraction (< 55%), which is difficult to distinguish from mild DCM in absence of LGE. In cases like this, the evaluation of systolic function during stress is of pivotal importance for differential diagnosis

50]. Therefore, dilated LV with reduced resting EF, may lead to misclassification of DCM. A useful parameter to distinguish the physiological adaptation in athletes from DCM is the increase in ventricular EF during the exercise; rarely demonstrated in DCM [51]. Recently, in-scanner real-time CMR protocol has been developed to assess the ventricular function during exercise [52], improving CMR capability to distinguish DCM from ventricle adaptation to training.

Moreover, patients with DCM often showed mid-wall LGE involving the interventricular septum [53]. Despite the high specificity, the absence of LGE does not exclude DCM. Native T1 mapping and ECV values were found to be higher in DCM in comparison with healthy athletes [54]. However, these data derived from a limited sample size study and need to be confirmed in a larger population.

Moreover, excessive trabeculation in athletes' heart raise concern about the potential diagnostic grey zone between left ventricle non compaction (LVNC) and exercise-induced remodeling.

LVNC is a condition characterized by a double-layered myocardial wall, with a thicker trabeculated layer compared to compacted wall and presence of deep intertrabecular recesses (Fig. 6) [55].

Pathognomonic clinical presentation of LVNC is heart failure, ventricular arrhythmia and systemic thromboembolism; however, the presentation can be variable according to the severity of disease.

Currently, the diagnostic challenge is to distinguish LVNC from adaptive hypertrabeculation, in the absence of accepted diagnostic criteria.

Hypertrabeculation is a phenotypic manifestation, often seen in several myocardial disorders [56]. Only a limited number of studies [57, 58] have investigated the mechanisms that lead to hypertrabeculation; apical trabeculae cause wall stress redistribution, which in turn may protect the heart from adverse aneurysmal remodeling [57] in order to achieve a higher stroke volume without an increase in longitudinal strain [58]. Moreover, it has been hypothesized that a failure in LV twist could trigger compensatory hypertrabeculation to facilitate ventricular emptying [58].

In 2015, Caselli et al. [59] recommending CMR for exclusion of LVNC in asymptomatic subjects without family history and EF < 50% and in subjects with EF > 50% and positive family history, ECG anomalies or ventricular tachyarrhythmia.

Established CMR diagnostic criteria for LVNC are:

- the ratio between trabeculated and compacted layer > 2.3 in end-diastolic long axis view, excluding the apex (Fig. 6) [60];
- trabeculated myocardial mass > 20% of the total myocardial mass of the left ventricle (Fig. 6) [60];
- maximal apical fractal dimension of > 1.3 [61].

Ancillary criteria are represented by the dilation of the left ventricle and the presence of late enhancement. Intracavitary thrombi among the prominent trabecular structure has also been reported.

Myocarditis

Myocarditis is responsible for 2–20% of sudden deaths in athletes [8]. It was diagnosed in up to 8% of SCD in athletes in post-mortem studies [62]. Diagnosis of myocarditis is based on clinical evaluation, lab tests, ECG, echocardiography and CMR [63].

CMR is able to non-invasively diagnose myocarditis based on the detection of the three main physiopathological phenomena occurring during myocardial inflammation such

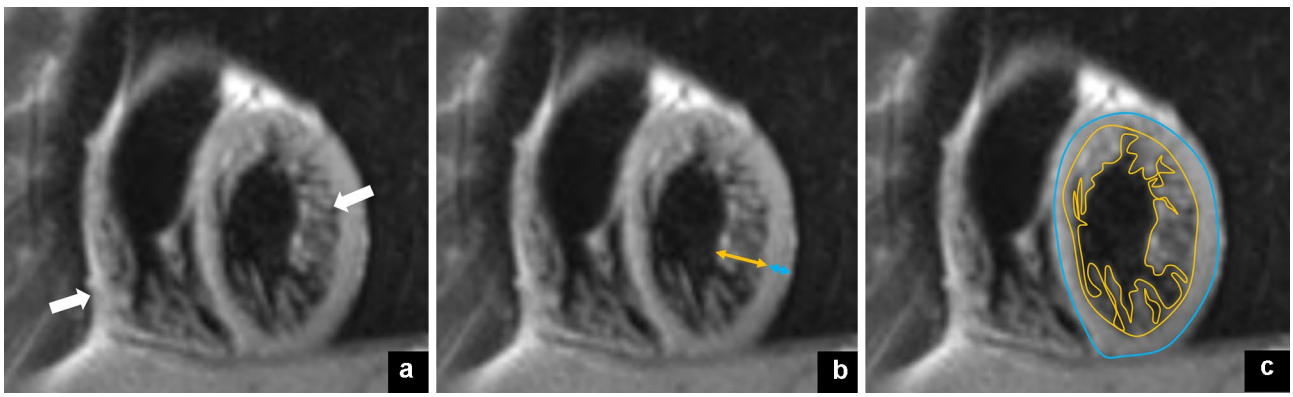

Fig. 6 Non-compaction cardiomyopathy. Two-chamber short-axis PD images show non compaction cardiomyopathy (**a**) involving both right and left ventricle (white arrows in **a**) with a ratio between trabeculated layer (yellow line in **b**) and compacted layer (blue line in **b**) equal to 3 (normal value < 2.3) and trabeculated LV myocardial mass > 20% of the total LV myocardial mass (trabeculated myocardium mass in yellow contours/ total myocardial mass in yellow plus blue contours in c)

as edema, hyperemia and necrosis/fibrosis (Fig. 7) [64, 65]. Traditional diagnostic criteria, the so-called Lake Louise Criteria (LLC) [64], showed a suboptimal diagnostic accuracy (close to 80%), poorer in chronic myocarditis. This is mainly due to the signal intensity-based approach for the evaluation of diffuse myocardial involvement; a, remote myocardium or skeletal muscle intensity, as reference tissue, with risk of false negative results in coexisting myocarditis [66]. Moreover, conventional imaging resulted prone to artifacts [66].

The recent introduction of mapping parameters in the diagnostic criteria [65] significantly improved CMR sensitivity in the detection of myocardial inflammation [65, 67], for the capability to identify subtle myocardial injury [68] and to distinguishing active from healing myocarditis [69], quantifying myocardial microstructural alteration with a pixel-wise approach, overcoming the limits of conventional LLC [66].

During the COVID-19 pandemic, signs of myocardial inflammation in asymptomatic or mildly symptomatic competitive athletes after COVID-19 were identified at CMR with variable prevalence (0%-15%) [70]. In a large cohort of 1597 US competitive collegiate athletes positive by polymerase chain reaction for SARS-CoV-2, CMR with updated LLC was found to improve the detection of myocarditis from 0.31%, based on symptom-based screening strategy, to 7.4% and 2.3% in clinical and subclinical myocarditis [70].

According to current recommendations from American Heart Association/American College of Cardiology and European Society of Cardiology [8, 71], the participation to competitive sport activities has to be refrained in those athletes with diagnosis of myocarditis and evidence of active inflammation until inflammation resolves in the follow-up CMR.

Athletes who are asymptomatic with no arrhythmias and with normal echocardiogram and exercise capacity may return to sport.

However, based on the additional information provided by CMR in SARS-CoV2 positive athletes, also in absence of other cardiac tests abnormalities, the potential benefit of CMR screening protocols has been advocated, and in particular the value of CMR imaging, prior to returning to sport after COVID-19 infection [70].

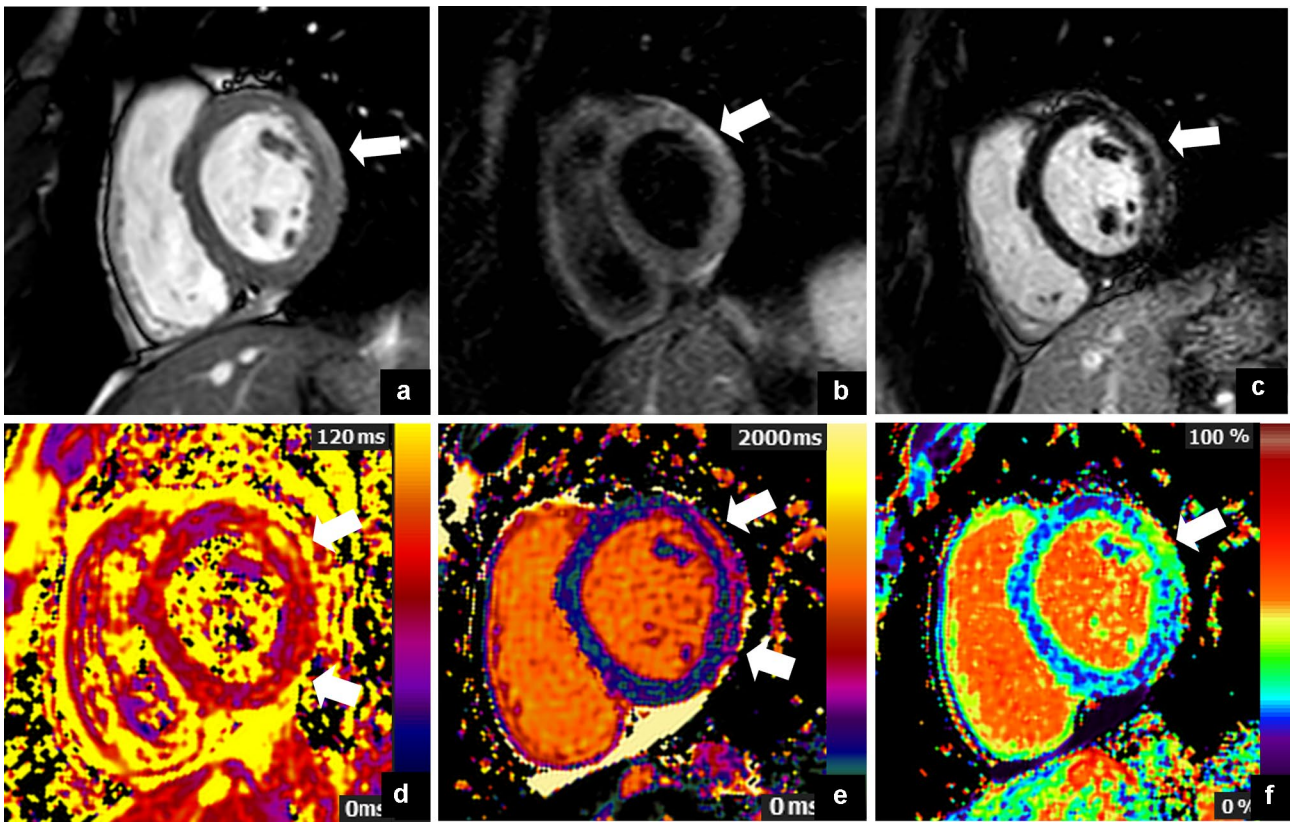

Fig. 7 CMR in myocarditis. CMR findings in an 18-years-old male with acute chest pain while playing soccer, associated with mild fever and pharyngodynia. Cine SSFP image shows a thin subepicardial area of hyperintensity on the basal lateral wall (arrow in **a**), corresponding to focal edema on STIR (arrow in **b**) and subepicardial scar (arrow in **c**). Native T1 (**d**), T2 mapping (**e**) and ECV (**f**) maps show altered values on the lateral wall (native T1: 1128 ms; T2: 61 ms; ECV: 31%). CMR findings suggestive of acute myocarditis

CMR was found to provide prognostic information in myocarditis. LGE was the best predictor of mortality [72] especially septal mid-wall involvement [73].

Myocarditis has to be distinguished by other non-ischemic cardiomyopathies including the left-dominant arrhythmogenic cardiomyopathy (LDAC) (Fig. 4) and sarcoidosis. CMR provides complementary information to clinical, genetic/histological and ECG data. CMR identifies fibrofatty replacement of LV in LDAC, typically with epicardial involvement and irregular epicardial borders on the lateral wall ("the rat-bite sign") [74], also associated with wall motion abnormalities. CMR also allows to distinguish myocarditis from cardiac sarcoid, the latter with typical hypertrophic phenotype and frequent septal involvement [75] and possible concomitant RV-LGE.

Arrhythmogenic bileaflet mitral valve prolapse

Mitral valve prolapse (MVP) is defined as > 2 mm displacement of one or both leaflets of the mitral valve beyond the annulus within the left atrium in end-systole. MVP affects 1–3% of the general population with 0.2–1.9% estimated 1-year risk of SCD and is responsible of 7% of SCDs in young adults according to the Italian cardiac pathology registry [76].The development of life-threatening arrhythmic events seems to be associated with prolapsing leaflet-induced papillary muscles/inferobasal left ventricle fibrosis due to mechanical traction and hyperadrenergic state (Fig. 8) [76]. Risk factors are: female sex, bileaflet prolapse, moderate-severe mitral regurgitation (MR), focal LV papillary muscle fibrosis, inferobasal fibrosis or diffuse subclinical interstitial fibrosis on CMR, mitral annulus disjunction (MAD), history of complex ventricular ectopy, T wave inversion in the inferior leads, ventricular arrhythmia arising from the LV and familiarity for SCD [77].

In particular, Carmo et al. found that a mitroanular disjunction > 8,5 mm as a strong predictor of non-sustained ventricular tachycardia (OR 10 95% CI 1.28–78.1) [78, 79].

Exercise has been associated to SCD in patients with MVP for increased sympathetic tone and worsening of MR [8]. Athletes with MVP should undergo exercise test and 24-h ECG and in case of alterations, CMR for detection of myocardial scars. Physical activity should be restricted to low-intensity sports in presence of any of the following risk factors: (a) prior arrhythmic syncope, (b) frequent and/or complex premature ectopic beats, (c) sustained or recurrent non-sustained ventricular tachycardia, (d) family history of SCD, (e) severe MR, (f) reduced LVEF (≤ 50%) and (g) prior thromboembolic events. In athletes with asymptomatic isolated MVP no sport restriction is required.

Coronary artery anomalies and atherosclerotic disease

Coronary anomalies are one of the main causes of SCD among young athletes [8]. SCD may occur in coronary anomalies with hemodynamic impact, such as anomalous left/right coronary artery from the pulmonary artery (ALCAPA/ARCAPA) or anomalous-origin of left- (AOLCA) or right- (AORCA) coronary artery from the opposite ("wrong") Valsalva sinus especially the so called "malignant" variants, typically characterized by intramural

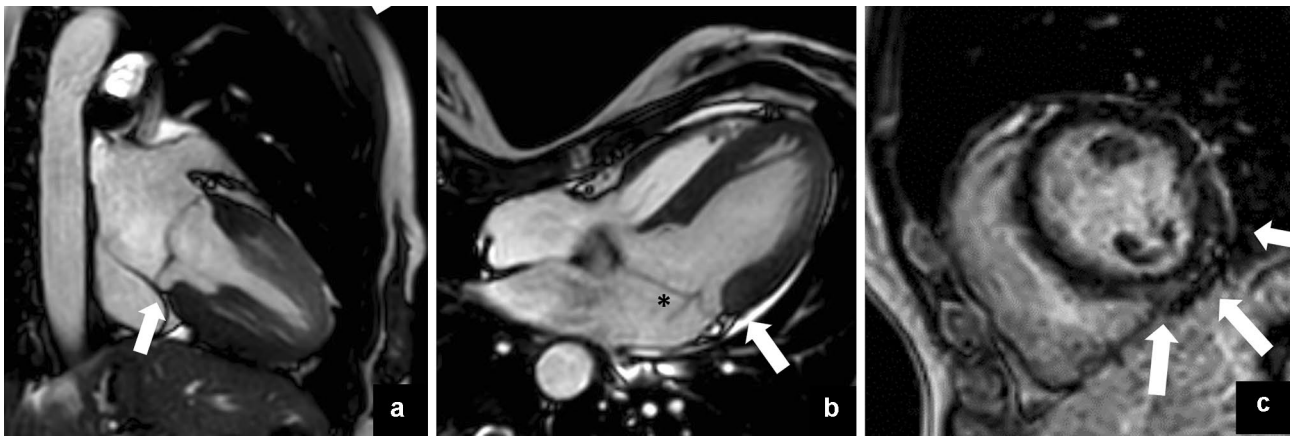

Fig. 8 Arrhythmogenic mitral valve prolapse. Cine images of a 45-years-old female with frequent BEV and non-sustained ventricular tachycardia (VT), show bileaflet mitral valve prolapse, mitroanular disjunction (arrow in **a**), systolic curling of lateral LV wall (arrow in **b**) and a small jet of mitral valve regurgitation (asterisks in **b**). LGE with non-ischemic pattern involves the inferior and infero-lateral basal wall (arrows in **c**). At elettroanatomic mapping, ventricular fibrillation was inducible, with subsequent implantation of a cardioverter defibrillator

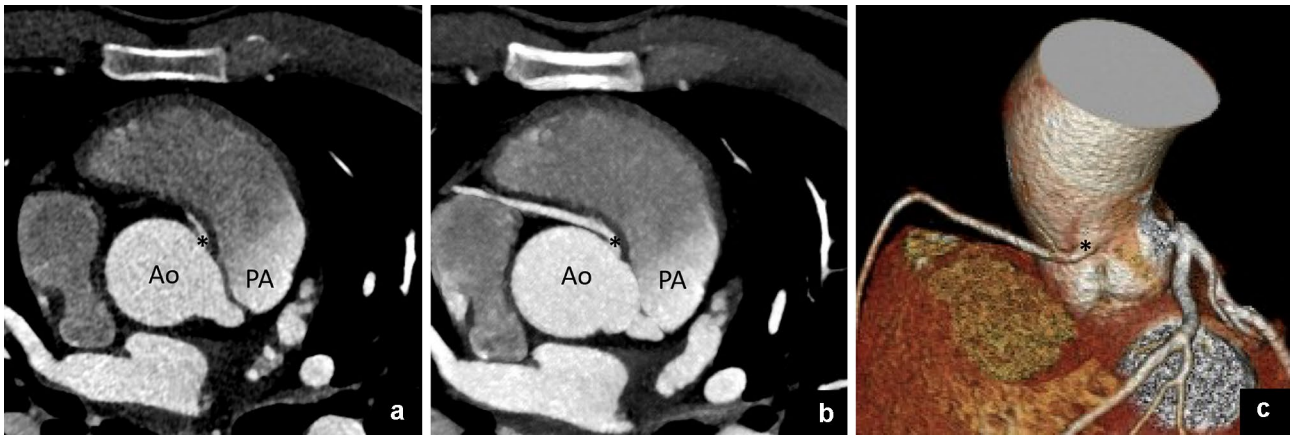

Fig. 9 Malignant origin of right coronary artery. Axial (**a**), axial-MIP (**b**) and 3D volume rendering (**c**) images show the presence of anomalous origin of the right coronary artery (*) from the left coronary sinus with malignant course between ascending aorta (AO) and the main trunk of the pulmonary artery (PA)

or interarterial course (Fig. 9), the 2nd cause of SCD in young athletes in USA and the 3rd in Italy [80].

Among master athletes, CAD is the most frequent cause of SCD during sports occurring in up to 80–90% at post-mortem evaluation, due to acute plaque rupture/erosion or complication of severe stenosis [8, 81].

Indication to cardiac imaging is guided by clinical evaluation of risk factors and maximal exercise stress test [8]. In cases of suspected CAD, advanced cardiac imaging is performed according to 2019 ESC guidelines for the management of chronic coronary syndrome [82]; coronary artery calcium score improved risk assessment and provides additional prognostic information for patients' risk stratification [82].

Cardiac imaging techniques allow to non-invasively identify coronary anomalies of origin and course, malignant variants, intramural course and fistulas and have improved the diagnosis of CAD over clinical risk score assessment, identifying a greater number of individuals with asymptomatic CAD.

CCTA is the non-invasive technique with highest sensitivity (91–99%) and specificity (74–96%), with excellent negative predictive value (NPV 97–99%) able to accurately exclude obstructive CAD.

CCTA is fundamental in selection of best therapeutic strategy together with clinical and ECG-findings, proposing restriction or suspension of sport activity or return to sport after treatment. CCTA is mandatory in the diagnostic-workflow together with TTE and stress-ECG in order to rule-out CAD and anomalous origin/course, especially in "master" athletes [80].

CMR can be considered an alternative to CCTA in young athletes for the exclusion of anomalies of origin and proximal course of the coronary arteries, without needing contrast agent and without ionizing radiation [83, 84]. Moreover, in master athletes with a borderline or uninterpretable exercise test result in which a more specific imaging stress test is recommended, stress-CMR should be considered as a valid alternative to SPECT, for its higher sensitivity in the identification of myocardial ischemia [85] with the advantage of higher spatial resolution which allows a layer-by-layer assessment [86].

Conclusion

Advanced cardiac imaging has a pivotal role in the assessment of structural alteration in competitive athletes and can distinguish physiological adaptation from congenital anomalies and cardiomyopathy; this is crucial in the early detection of athletes at risk of SCD. The addition of mapping parameters may further improve CMR diagnostic capability in identifying cardiomyopathy at earlier stages.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The manuscript does not contain clinical studies or patient data.

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