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STATE-OF-THE-ART REVIEW

Arrhythmogenic Cardiomyopathy or "Athlete's Heart"?

A Systematic Approach to Differential Diagnosis

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ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) is a heritable cardiac condition, which may lead to fatal arrhythmias, especially during intense exercise. Long-term regular exercise is associated with a spectrum of physiological cardiac adaptations, some of which may overlap with phenotypic features of ACM, thereby complicating the distinction between benign athletic remodeling and early disease expression. This overlap presents a significant diagnostic challenge, as misclassifying pathological changes as physiological can delay appropriate risk stratification and management. By contrast, overdiagnosis of cardiomyopathy in healthy athletes may lead to unnecessary restriction from sport and psychological distress. The complexities in the differential diagnosis may be mitigated by embracing a comprehensive and systematic approach, including a thorough assessment of family and personal history, and a careful interpretation of the electrocardiogram, with further investigations to be requested if suspicion of an underlying disease is raised. This review provides a comprehensive analysis of the differential diagnosis between physiological cardiac adaptations and pathological changes that raise the suspicion of ACM, highlighting red flags and benign findings to rationalize clinical management. (JACC Clin Electrophysiol. 2025;■:■-■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Arrhythmogenic cardiomyopathy (ACM) is a heritable cardiac condition, characterized by progressive fibro-fatty replacement of ventricular myocytes.[1,2] This condition can lead to heart failure, sustained ventricular arrhythmias (VAs), and sudden cardiac death (SCD).[3-5] In some cases, SCD may be the first tragic manifestation of ACM in young, apparently healthy individuals.[6,7]

The long-term benefits of regular exercise on promoting cardiovascular health are well established.[8] However, engaging in intense exercise may be deleterious in individuals with underlying cardiovascular disease, and a tailored approach to exercise in these patients is appropriate.[9] Long-term athletic training is associated with a series of changes in cardiac structure and function.[10] These include bradycardia, sinus arrhythmia, prominent QRS voltages on the electrocardiogram (ECG),[11,12] dilation of cardiac chambers, and increased left ventricular (LV) wall thickness.[13-17] The overlap between ECG and

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ABBREVIATIONS AND ACRONYMS

ACM = arrhythmogenic cardiomyopathy

CMR = cardiac magnetic resonance

ECG = electrocardiogram

ETT = exercise tolerance testing

LBBB = left bundle branch block

LGE = late gadolinium enhancement

LQRS = low QRS

LV = left ventricle/ventricular

LVEDD = left ventricular end-diastolic diameter

PVB = premature ventricular beat

RBBB = right bundle branch block

RV = right ventricle

RVOT = right ventricular outflow tract

SCD = sudden cardiac death

TWI = T-wave inversion

VA = ventricular arrhythmias

structural/functional manifestations of the "athlete's heart" and of ACM may result in challenges in the differential diagnosis.[2]

Distinguishing physiological adaptation from ACM is critical, as sustained high-intensity exercise may act as a disease-modifying factor in individuals with ACM.[6] This is particularly evident in carriers of pathogenic variants in PKP2, who appear more susceptible to exercise-induced phenotypic expression and adverse outcomes.[18] Consequently, misclassification of pathological findings as benign athletic remodeling may lead to inappropriate reassurance and sustained high-level exercise, with potentially severe consequences.

In this narrative review, we discuss the challenges that are often encountered in the differential diagnosis between physiological adaptation to exercise and ACM, and we attempt to provide an algorithm aimed at streamlining clinical management (**Central Illustration**).

HIGHLIGHTS

- Differentiating ACM from physiological adaptation in athletes is essential to prevent exercise-related sudden cardiac death.
- A systematic, multiparametric approach enhances diagnostic accuracy and facilitates early detection of pathology in athletic individuals.
- Integration of ECG findings, advanced imaging, family history, and genetic testing helps to identify red flags suggestive of ACM.
- Artificial intelligence holds promise for improving early recognition and risk stratification in ACM, though further validation is needed before widespread clinical adoption.

ARRHYTHMOGENIC CARDIOMYOPATHY: FROM DEFINITION TO DIAGNOSIS

Historically, ACM has been defined as a condition affecting solely the right ventricle (RV). During the early 1980s, the disease was traditionally referred to as "arrhythmogenic right ventricular dysplasia" since the condition was initially thought to be congenital and to affect exclusively the RV.[19,20] A few years later, a study based on autoptic findings of young individuals who experienced SCD in the Veneto region in North-East Italy, demonstrated distinct histopathological features including progressive RV myocyte degeneration, necrosis, inflammation, and fibro-fatty replacement.[21,22] As a result of this and other studies that confirmed the primary heart muscle involvement of this condition, the nomenclature has been modified to "arrhythmogenic right ventricular cardiomyopathy."

In the following years, the heritable nature of the condition has been progressively established, leading to the discovery of several genes involved and specifically the ones encoding desmosomal proteins.[23,24]

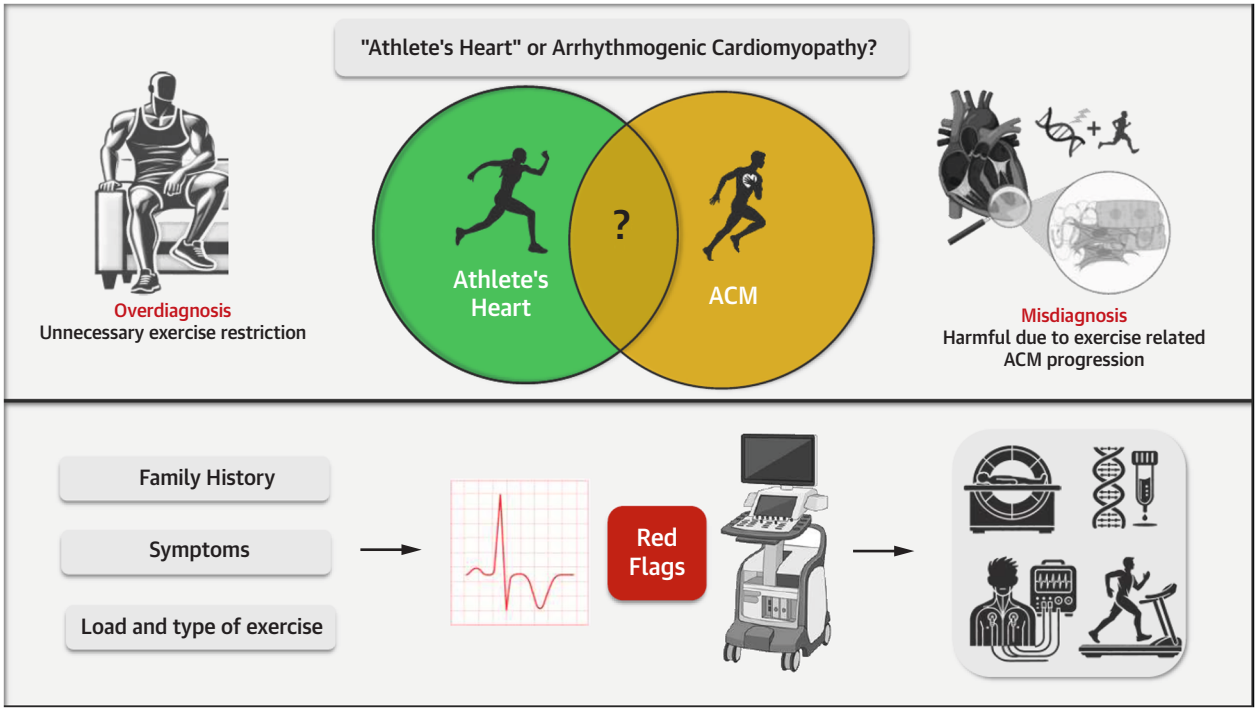
Over the past decade, through advances in diagnostic investigations, such as cardiac magnetic resonance (CMR), genetics, and cardiac autopsy, a frequent involvement of both ventricles has been progressively demonstrated, and the nomenclature has changed again, into "arrhythmogenic cardiomyopathy."[6,23,25-27]

The prevalence of ACM is estimated to be between 1:2,000 and 1:5,000.[6] ACM typically manifests between the second and fourth decade of life, while being uncommon in adolescents and children.[26,28-32]

Despite substantial advancements made in understanding the pathophysiological mechanisms underlying the disease, accurate diagnosis remains a challenge.[21,33] The efforts aimed at formulating a comprehensive set of clinical criteria for the diagnosis of ACM, resulted in the development of the Task Force Criteria published in 1994 and revised in 2010. The Task Force Criteria integrate a series of ECG, structural, functional, histopathological, and familial features of the disease.[34] The 1994 and 2010 criteria were largely based on the RV-dominant phenotype of the disease because a common LV involvement was not yet well known at that stage. The most recent international criteria include the LV-dominant phenotypes, incorporating tissue characterization on CMR.[21,23,34,35] ECG and CMR features of ACM are displayed in **Figure 1**. A strong link between intense exercise and severity of ACM phenotype has been shown by several, mostly retrospective studies, particularly in individuals with desmosomal mutations.[18,36]

ACM is strongly associated with exercise-induced SCD among athletes who died suddenly.[28] Several studies have shown that the prevalence of malignant

CENTRAL ILLUSTRATION **Distinguishing Athlete's Heart From Arrhythmogenic Cardiomyopathy**



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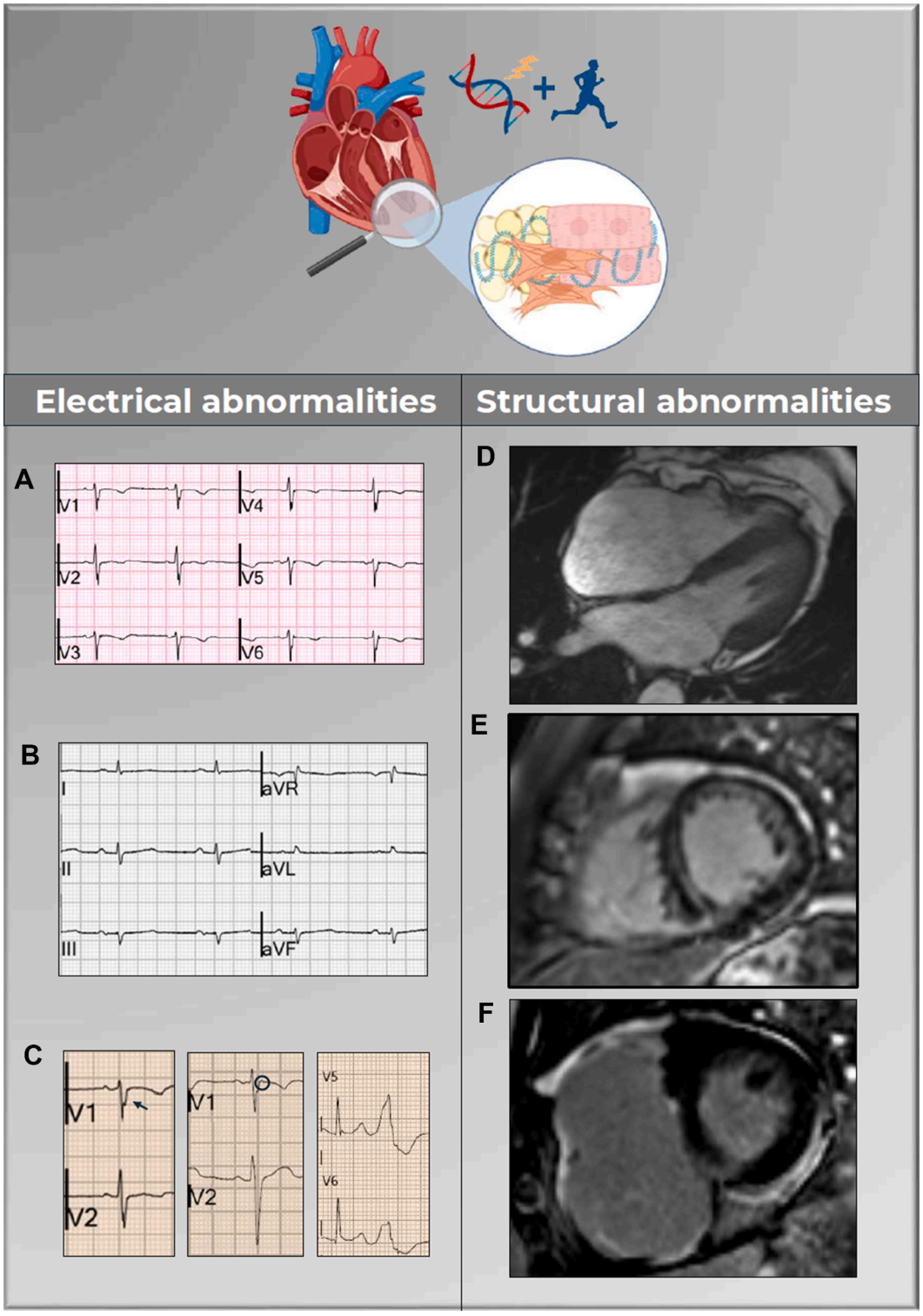
Distinguishing athlete's heart from arrhythmogenic cardiomyopathy (ACM) presents a diagnostic challenge, given the phenotypic overlap between physiological cardiac remodeling and early-stage pathological changes. This overlap may lead to misclassification and unwarranted restriction from competitive sports. A systematic approach incorporating a detailed personal and familial history, careful analysis of exercise modality and intensity, and scrutiny of red flag findings on electrocardiography and echocardiography is essential. When ambiguity persists, advanced imaging and genetic testing may provide critical differentiation, ensuring an accurate distinction between adaptive and pathological myocardial changes.

arrhythmias and RV systolic impairment appear to be higher in those patients who engage in competitive sport with respect to sedentary counterparts.[29,32] A growing body of retrospective data supports an association between high-intensity exercise and disease severity in ACM, particularly among individuals with desmosomal mutations. This link is underscored by studies showing a higher prevalence of malignant arrhythmias and RV dysfunction in competitive athletes compared with their sedentary counterparts.[18] However, much of the current evidence is observational, and causality remains difficult to establish definitively. Key limitations include retrospective study design, selection bias, and heterogeneity in exercise exposure definitions and genetic backgrounds. Moreover, the threshold at which exercise becomes deleterious and whether specific exercise modalities confer differing levels of risk are still areas of active investigation. As such, although high-intensity physical activity is widely considered a negative modifier of the ACM phenotype, particularly in genetically predisposed individuals, further prospective and mechanistic studies are needed to refine exercise recommendations and better stratify risk on a personalized basis.[37]

PHYSIOLOGICAL ADAPTATION TO EXERCISE IN ATHLETES

Athletes often exhibit a plethora of physiological electrical, and structural cardiac changes as a result of regular exercise.[38,39] Determinants of cardiac remodeling include several factors such as sport discipline, exercise intensity, body size, sex, age, and

FIGURE 1 **Pathophysiology and Clinical Features of ACM**



Genetic predisposition, in some cases in combination with environmental factors, such as intense exercise, may lead to fibro-fatty replacement of the myocardium, providing a substrate for ventricular arrhythmias. (A) Note the widespread T-wave inversion on the precordial leads. (B) Note the low QRS voltages on the limb leads. (C) Note in the left box, a terminal activation duration of QRS ≥55 ms in V_1 (arrow), in the middle box, epsilon wave in V_1 (circle); in the right box, a premature ventricular beat with wide QRS. (D) Steady-state free precession cardiac magnetic resonance imaging, cine 4-chamber view, revealing an aneurysm of the right ventricular free wall. (E) Short-axis view at mid-ventricular level, mid-wall ring-like late gadolinium enhancement pattern (in this case in the context of a DSP pathogenic variant); (F) Short-axis view at basal level, showing severe right ventricular dilation with LGE presence within the RV free wall.

ethnicity. Endurance sports appear to have the most profound impact on electrical and structural changes.[13,38,40]

The ECG of highly trained athletes may show signs of increased vagal tone, such as sinus bradycardia, sinus arrhythmia, first degree atrioventricular block, or nocturnal second degree atrioventricular block, Mobitz type I. Prominent QRS voltages, incomplete right bundle branch block (RBBB), and repolarization abnormalities, such as T-wave inversion (TWI), in the anterior leads are also relatively common.[12,41] Early repolarization patterns with TWI extending to lead V_4, particularly when preceded by convex ST-segment and J-point elevation, have historically been described as more prevalent among athletes of African and Afro-Caribbean descent.[42] However, this pattern has also been observed in non-Black athletes, particularly younger individuals, and there is no evidence to suggest that its presence is pathological.[43-45] As highlighted by Krishnan et al[46] in *JAMA Cardiology*, race is a social construct rather than a biological determinant, and the early repolarization-TWI pattern should not be interpreted through a race-based lens. The benign nature of this ECG variant has been consistently demonstrated, perhaps with less longitudinal studies on Caucasian athletes.

Endurance athletes often exhibit an harmonic dilatation of the LV and RV.[47,48] A study on Italian Olympic athletes across 38 sports, mostly involved in endurance disciplines, showed that 14% of male Olympic athletes exhibit a left ventricular end-diastolic diameter (LVEDD) >60 mm.[49] As far as the RV is concerned, similar findings were observed in another study, where 23% athletes exceeded the thresholds for RV dilatation, set by the American Society of Echocardiography, and among them, endurance athletes exhibited the most pronounced RV remodeling.[50]

Female athletes exhibit smaller absolute LV sizes.[51] However, when adjusted for body surface area, their indexed LV dimensions are higher than those of male athletes.[52] Similarly, in adolescent athletes, the LVEDD usually falls between 40 and 60 mm with <20% reported to have measurements over 54 mm, with values above 60 mm being quite rare.[53] In Afro-Caribbean athletes (including adolescent athletes), LV wall thickness appears to be higher than in white counterparts.[42] LV dilatation may be accompanied by a decline of left ventricular ejection fraction (LVEF) at rest on echocardiogram in endurance athletes. An observational study of elite cyclists who participated in the Tour de France in 1995 and 1998 found that 51% of them exhibited LV dilatation (LVEDD >60 mm), and 18% a LVEF <55%.[54]

DIFFERENTIAL DIAGNOSIS: THE NEED FOR A COMPREHENSIVE APPROACH

A stepwise, comprehensive approach, taking in consideration multiple variables, from family and personal history to ECG and cardiac imaging, may resolve the many challenges in the differential diagnosis between the 2 entities. Knowledge and ability to recognize "red flags" is relevant to this exercise (**Figure 2**).

FAMILY AND PERSONAL HISTORY

Cardiac assessment of athletes should always start from an inquisitive approach to personal and family history.

PERSONAL HISTORY. Although fatal arrhythmias may be the first manifestation of ACM, the most common symptoms that should raise the suspicion of an underlying cardiomyopathy are palpitations, presyncope, and syncope, particularly during exercise and reduced exercise tolerance.[55] Syncope during exercise should always be given the appropriate attention, with further comprehensive cardiac investigations aimed at ruling out an underlying cardiac condition. Recurrent episodes of myocarditis, manifesting with chest pain, ECG changes and troponin rise, should raise the suspicion of ACM as this condition may present with "hot phases" characterized by myocardial inflammation.[28,56]

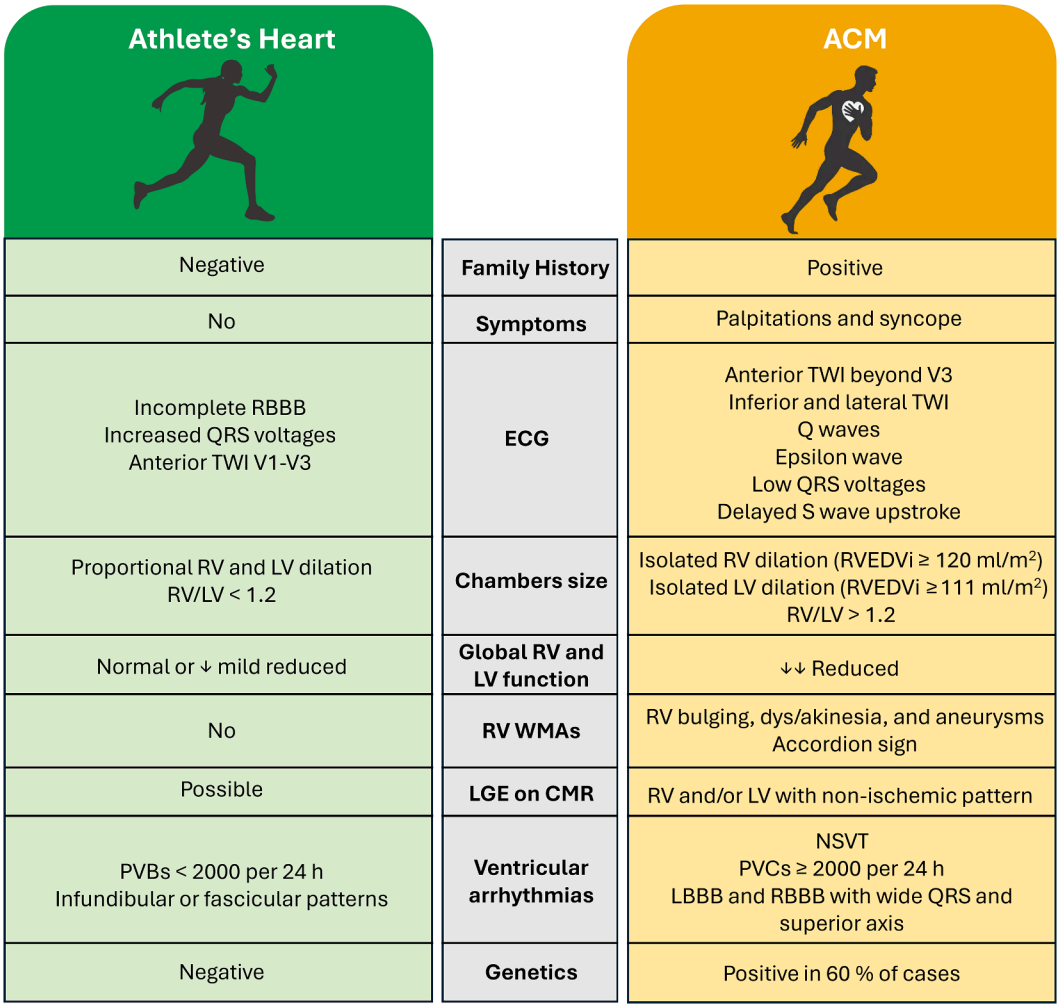
The disease may not affect only the heart, especially in certain genetic types. ACM may be part of Naxos disease, caused by a *JUP* gene mutation, where cutaneous features such as palmoplantar keratosis and woolly hair may be predominant.[19,57] Patients affected by Carvajal syndrome, which is caused by a defect in the desmoplakin (*DSP*) gene, show similar cutaneous features.[28,58]

FAMILY HISTORY. A detailed family history is crucial to raise the suspicion of ACM. The collection of at least a 3-generations pedigree investigating the possible presence of familial premature cardiovascular disease and sudden death may suggest a strong predisposition to develop this condition.[31] Family screening of first-degree relatives of ACM is recommended.

THE 12-LEAD ECG

Interpretation of the ECG is often challenging in athletes, as physiological changes may be erroneously deemed as pathological and suggestive of a

FIGURE 2 **Red Flags for Differentiating Athlete's Heart From ACM**

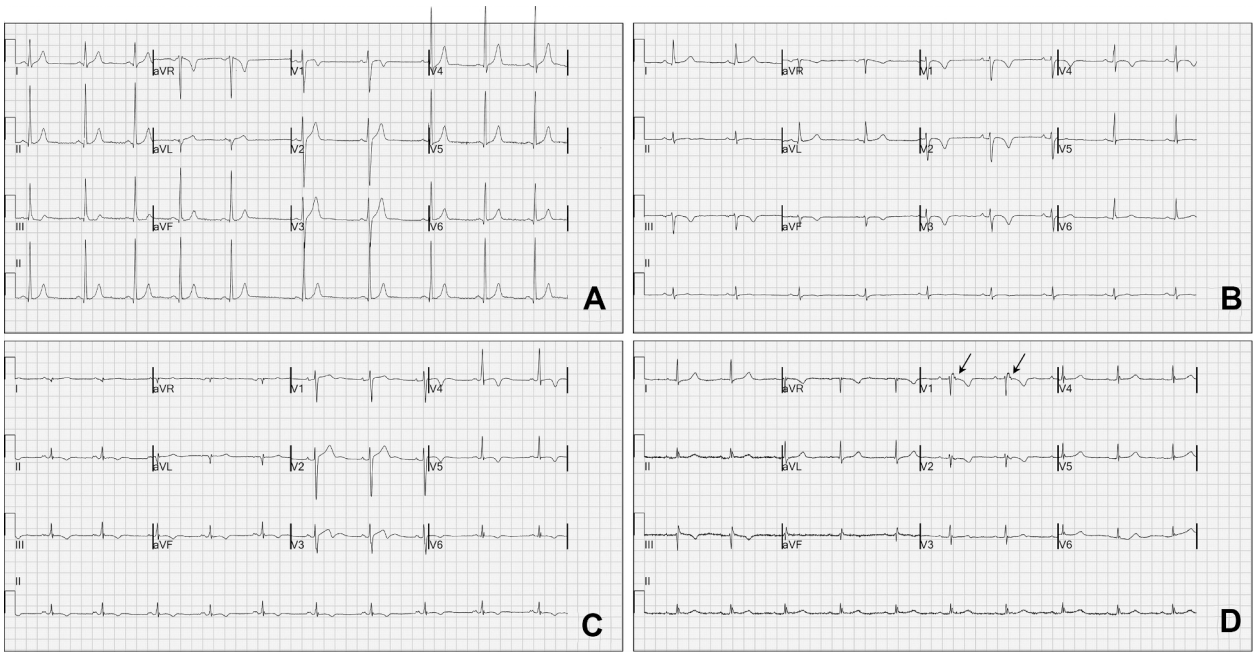


ACM = arrhythmogenic cardiomyopathy; CMR = cardiac magnetic resonance; ECG = electrocardiogram; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LV = left ventricle; LVEDVi = left ventricular end-diastolic volume index; NSVT = nonsustained ventricular tachycardia; PVBs = premature ventricular beats; RBBB = right bundle branch block; RV = right ventricle; RVEDVi = right ventricular end-diastolic volume index; SCD = sudden cardiac death; SVT = sustained ventricular tachycardia; TWI = T-wave inversion; WMAs = wall motion abnormalities.

cardiomyopathy and vice versa (Figure 3). ECG abnormalities are reported in up to 81% of patients with ACM.[59] A systematic approach to the ECG, interpreting findings in the clinical context, can often be helpful to avoid confusion and may support the appropriate clinical management (Figure 2).

ANTERIOR TWI. Anterior TWI is the most common ECG abnormality in ACM. More than one-half of patients with ACM exhibit this feature.[59] However, anterior TWI is relatively common in healthy young individuals and athletes.[42] TWI in leads V_1 to V_4, when preceded by J-point elevation and convex ST-segment elevation, has historically been described as a benign variant (Figure 4A) more frequently observed in male athletes of African or Afro-Caribbean descent.[42] Nonetheless, this pattern has also been documented in non-Black athletes, especially younger individuals,[44,45] and there is no evidence to suggest that its presence is pathological based on race or ethnicity.[46] Calore et al[60] compared the ECGs of young athletes with TWI and of patients with cardiomyopathies and found that J-point elevation ≥1 mm preceding anterior TWI confined

FIGURE 3 **ECG Findings in Healthy Elite Athletes and in Patients With ACM**



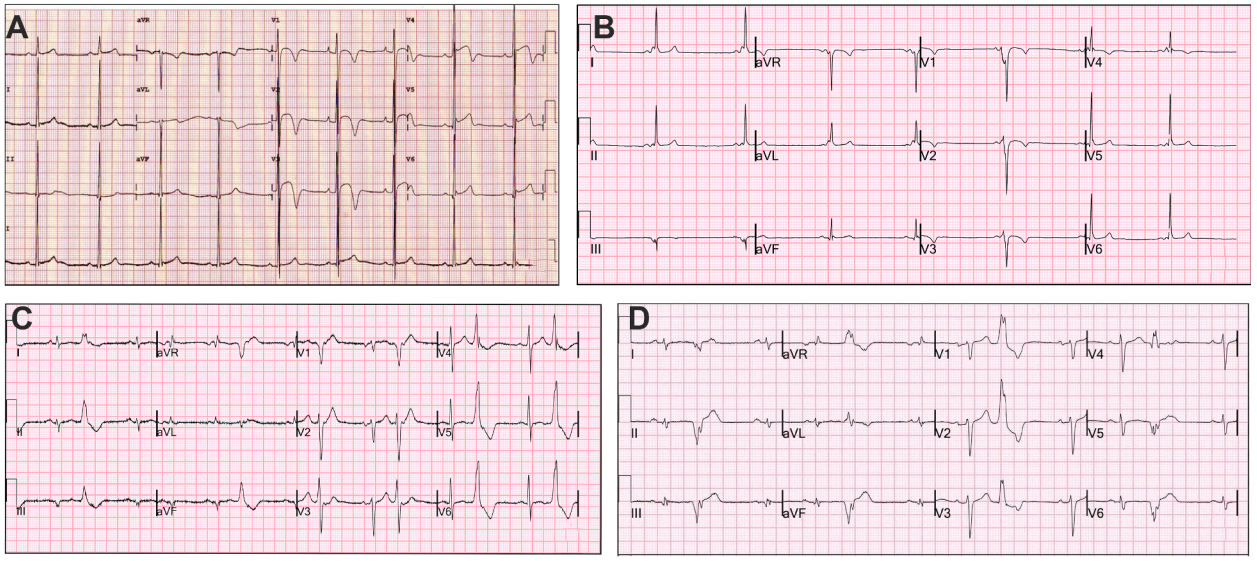
(A) In a 27-year-old healthy basketball elite athlete, the ECG shows respiratory sinus arrhythmia, prominent QRS voltages, and TWI limited to leads III, aVR, and V1. (B) In a 30-year-old man with ACM, the ECG shows TWI in V_1 to V_4 with J-point elevation <1 mm and in lead III. (C): In a 51-year-old recreational tennis player, the ECG shows low QRS voltages in the limb leads and diffuse TWI. (D) In a 44-year-old runner, the ECG shows an epsilon wave (arrows) in V_1 and V_2 leads. The athlete was eventually diagnosed with ACM. Abbreviations as in Figure 2.

to lead V_4 reliably excluded an underlying cardiomyopathy. By contrast, J-point elevation <1 mm and TWI extending beyond lead V_4 were signs that were associated with a diagnosis of ACM. The 2 cohorts were not age and ethnicity matched because a majority of the athletes were young, male, and of African and Afro-Caribbean descent, whereas patients with ACM were older and mostly Caucasian. By contrast, Brosnan et al[61] compared the ECGs of athletes with anterior TWI and of patients with ACM and found no significant difference in the proportion of individuals exhibiting J-point elevation ≥1 mm in the 2 groups. Finocchiaro et al[59] compared features of anterior TWI in young healthy individuals (athletes and sedentary) who were investigated with comprehensive cardiac investigations, and in patients with ACM. The presence of J-point elevation <1 mm was a poor discriminator in distinguishing ACM. Overall, although J-point elevation <1 mm preceding TWI may raise the suspicion of ACM (Figure 4B), it cannot be exclusively relied on, due to its significant prevalence also in healthy individuals. By contrast, a significant J-point elevation was highly suggestive of physiological findings in keeping with "athlete's heart."[59]

TWI IN INFERIOR AND LATERAL LEADS. Anterior TWI beyond V_4 should be considered a sign of pathology, and therefore, appropriate further investigations are warranted.[59,61] Lateral TWI (leads I, aVL, V_5, and/or V_6), especially if associated with low QRS (LQRS) voltages, may be a sign of ACM with predominant LV involvement.[35] Furthermore, multiple studies have demonstrated inferior TWI (leads II, III, and aVF) more frequently coexist with anterior TWI in patients with ACM conversely, as compared with healthy athletes.[55,59,61] The clinical significance of isolated inferior TWI remains unclear, especially in the absence of cardiac symptoms or of family history of premature cardiac disease.[62]

PATHOLOGICAL Q WAVES. Pathological Q waves are defined as a Q/R ratio ≥0.25 or ≥ 40 ms in duration in 2 or more leads excluding leads III and aVR.[12] According to Zaidi et al,[55] pathological Q waves are present in ACM in 8.6% of cases. This feature should always be investigated appropriately if found in ≥2 contiguous leads (except III and aVR) and is considered to be a sign of disease unless proven otherwise.[12,55]

FIGURE 4 Electrocardiographic Features Distinguishing Physiological Adaptation From ACM-Related Abnormalities



(A) Anterior TWI in V_1 to V_4 with J-point elevation in an athlete, consistent with exercise-induced repolarization changes; (B) and Anterior TWI in V_1 to V_4 without J-point elevation, with S-wave prolongation and an ECG pattern that is suggestive of ACM; (C) Benign premature ventricular beats (PVB) with LBBB and inferior axis pattern, consistent with an origin from the right ventricular outflow tract; (D) High-risk PVB with RBBB morphology and superior axis. Abbreviations as in Figure 2.

PREMATURE VENTRICULAR BEATS. Premature ventricular beats (PVBs) are relatively common in athletes. According to the international recommendations for electrocardiographic interpretation in athletes, the presence of ≥2 PVBs on a resting 12-lead ECG in athletes should warrant further cardiac investigations.[12] The presence of ≥1 PVBs on a 12-lead ECG were found in under 20% of ACM cases.[26,59,61] The index of suspicion of ACM should be high if an athlete exhibits an increasing burden of PVBs during exercise.[6]

Analysis of the morphology of the PVBs is crucial to infer their site of origin. Although benign PVBs can originate from multiple cardiac structures, the most common are the fascicles of the left bundle, the right ventricular outflow tract (RVOT), the LV outflow tract/aortic cusps, and the anterior mitral annulus. Origin from these sites is associated with a lower probability of underlying structural heart disease, particularly in asymptomatic athletes.[41,63,64] By contrast, PVBs with a broad RBBB pattern (QRS >130 ms) and superior axis are uncommon among athletes. Recent studies have indicated an association between this PVB pattern and underlying LV scar and possibly ACM.[41,63,65-67]

LQRS VOLTAGES. LQRS voltage is defined as peak-to-peak QRS amplitude <0.5 mV in all limb leads.[41,68] Recent studies have shown that isolated LQRS voltages are extremely rare in athletes and instead a relatively common in patients with ACM, observed in around <15% of cases.[59,68] Furthermore, isolated LQRS voltages were slightly more common in female athletes than in their male counterparts.[68] The presence of LQRS voltages may be a sign of myocardial fatty infiltration or of replacement fibrosis.[1,68]

EPSILON WAVES. Epsilon waves are defined as small-amplitude positive potentials and may be seen in leads V_1 to V_3, immediately after the end of the QRS complex.[41] A recent study showed that epsilon waves were found in up to 7% of ACM cases when associated with anterior TWI.[59] However, although it may be a specific ECG sign towards ACM, it is not a sensitive ECG marker, with large interobserver variability reported. Hence, without other ECG features, isolated epsilon waves should be interpreted with caution.[1,19,21]

DELAYED S-WAVE UPSTROKE. A delayed S wave (measured from the nadir of the S wave to the end of the QRS complex) >55 ms in leads V_1 to V_3 in combination with anterior TWI and in the absence of complete RBBB should raise the suspicion of ACM.[41,59] A recent study showed that S-wave delay in

V_2 (>55 ms) in combination with anterior TWI sign was present in over a quarter of individuals with ACM, and in none of the healthy individuals with anterior TWI.[59]

CHILDREN AND ADOLESCENTS. Anterior TWI in the right precordial leads (V_1-V_3) in children and adolescents prior to puberty is considered a benign finding (juvenile pattern).[12,69] If anterior TWI persists after the age of 16 years, then further cardiac investigations are warranted.[12,62] Papadakis et al[43] showed that TWI extending beyond lead V_2 was extremely rare and almost confined to predominantly Caucasian athletes aged <16 years old. By contrast, only 0.2% of male athletes aged ≥16 years exhibited TWI beyond lead V_2. At 1-year follow-up, TWI disappeared in most of the very young individuals who were showing this feature on the first ECG.[69]

ECG SIGNS OF LV INVOLVEMENT. The 12-lead ECG provides essential insights that help to distinguish physiological adaptation from pathological myocardial remodeling. In addition to its role in detecting disease, the ECG can guide clinicians in localizing the predominant site of ventricular involvement, thereby refining diagnostic strategies. In ACM, RV involvement is typically characterized by T-wave inversions in the right precordial leads (V_1-V_3), a RBBB pattern, QRS prolongation >110 ms, and epsilon waves in the same distribution. Additionally, delayed terminal activation exceeding 55 ms in the right precordial leads is often observed. These ECG patterns are commonly associated with ventricular arrhythmias exhibiting a left bundle branch block (LBBB) morphology and a vertical or horizontal axis. By contrast, LV-predominant forms may present with a LBBB or left-axis deviation, low limb-lead voltages, early R-wave transition in the precordial leads, and TWI in lateral or inferior leads. Epsilon-like deflections may also be seen outside the typical right precordial distribution. In these cases, ventricular arrhythmias often display a RBBB morphology with a superior axis. These diagnostic features, described in the Padua criteria[35] and expanded upon by Mascia et al,[70] enhance the specificity of clinical evaluation and should prompt further imaging and genetic investigations when indicated.

THE ROLE OF IMAGING

Cardiac imaging is crucial in the differential diagnosis between physiological cardiac adaptation to exercise and ACM. Echocardiography has limited sensitivity due to its lower spatial resolution and lack of a 3-dimensional view, especially to evaluate the complex anatomy of the RV. By contrast, CMR offers a better spatial resolution and 3-dimensional views.[71,72] Echocardiography remains essential due to its widespread availability, ease of reproducibility, versatility, and cost-effectiveness.[72]

ECHOCARDIOGRAPHY. Accurate assessment of LV and RV size and function is crucial in order to identify possible early pathological changes associated with ACM.

RV size can be estimated by assessment of RVOT diameters in parasternal long- and short-axis views, RV end-diastolic and end-systolic areas, and RV basal and mid-cavity diameters on apical views.[73] RV dilation is common, especially in endurance athletes, and it is typically global, proportional with the other chambers, in the absence of regional wall motion abnormalities.[36,74] By contrast, RV dilation that is disproportionate to LV should raise the suspicion of a pathological process. Regional wall motion abnormalities may be present in the absence of significant dilatation and may point toward a diagnosis of cardiomyopathy, in the appropriate clinical context.[17]

The assessment of global RV function can be difficult, and a RV-focused apical view should be used in addition to standard apical views to allow better visualization of the RV free wall.[75] A comprehensive evaluation includes the measurement of tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived RV peak systolic velocity, and RV fractional area change.[73] Since RV dilation may be a sign of physiological cardiac adaptation, D'Ascenzi et al[76] proposed normal reference values for RV echocardiographic parameters, based on sex, type of sport, and body surface area. Specifically, for endurance athletes the normal reference values were identified as RVOT <17 mm/m^2 (parasternal long-axis) or <18 mm/m^2 (parasternal short-axis) for both sexes, and an RV fractional area change >35% for males and >39% for females.[76]

A key point in confirming the presence of ACM is the detection of RV regional wall motion abnormalities (akinesia, dyskinesia, and bulging). These are not easily identifiable through echocardiography, and often require CMR assessment.[35,36,77]

The use of RV strain is increasingly growing with the aim of differentiating between athletic adaptation and pathology in "grey zone" cases. In ACM patients, RV strain is typically reduced, whereas in athletes, it usually remains normal.[78] However, endurance athletes may show a slight reduction in RV strain,[79] and it tends to be more pronounced in the basal RV segment, especially in athletes with RV

dilation.[80] Additionally, the presence of mechanical dispersion in RV contraction, which is typically absent in healthy individuals, has been identified as an early indicator of ACM and a predictor of future arrhythmic events.[81,82]

CARDIAC MAGNETIC RESONANCE. CMR offers the added benefit of high spatial resolution imaging and dedicated protocols (such as RV stack views and sequences targeting the RV inlet and outflow tract).[83] This test provides accurate quantification of RV and LV volumes and systolic function, and identifies regional wall motion abnormalities that may be missed by echocardiography (**Figure 5**).[83] RV enlargement in athletes is usually accompanied by concomitant LV dilation, reflecting a symmetrical adaptation of the heart to the hemodynamic changes induced by training.[17] A ratio of RV to LV end-diastolic volume >1.2 is unlikely to be physiological and instead suggests an underlying pathology.[55,84] A meta-analysis based on 27 studies with 983 healthy male athletes aged 18 to 55 years proposed normal values for ventricular dimensions and function assessed by CMR. RV and LV end-diastolic volumes, respectively, of <120 mL/m^2, and <111 mL/m^2, RV ejection fraction >54%, and LVEF >59% have been proposed as reference values in endurance athletes.[85] In general, RV ejection fraction ≤45% serves as a strong indicator of underlying pathology.[55,84]

Wall motion abnormalities should raise the suspicion of cardiac disease. A focal "crinkling" or microaneurysms within the RV free wall, usually at the level of the sub-tricuspid region, has been increasingly recognized as a sign of ACM. This distinctive feature is highly specific for ACM and is predominantly linked to mutations in the PKP2 gene and has been named "accordion sign,"[86]

Late gadolinium enhancement (LGE) is commonly found in ACM.[87] The assessment of LGE in the RV is challenging due to its thin wall and prominent trabeculations.[88] Patterns of LGE distribution may vary according to the underlying genetic status.[87] Patients with mutations in DSP and filamin C (FLNC) genes often exhibit a characteristic subepicardial, "ring-like" scar pattern. Moreover, patients with DSP mutations often show an involvement of the LV with extensive fibrosis that largely exceed the degree of ventricular systolic dysfunction.[89,90]

Recent studies have shown that LGE suggestive of myocardial fibrosis may be present in healthy athletes. This finding may be the result of repetitive exposure to high-intensity activity that could induce myocardial microinjury and increase ventricular wall tension leading to myocardial fibrosis.[91] In a recent meta-analysis encompassing 12 studies, LGE was reported in 21% of endurance athletes, significantly higher than the 3% in the control group (sedentary individuals or those engaging in low physical activity levels). Although LGE localized to the RV hinge points was the most common pattern in both groups, in 40% of endurance athletes exhibiting LGE, the pattern was subepicardial and mid-wall.[92] The prognostic significance of these findings is still unclear.[91]

T1-weighted images may reveal increased myocardial T1 values, which may predate the development of an overt phenotypes, and therefore, may serve as a useful parameter in the assessment of the proband first-degree relatives.[93,94]

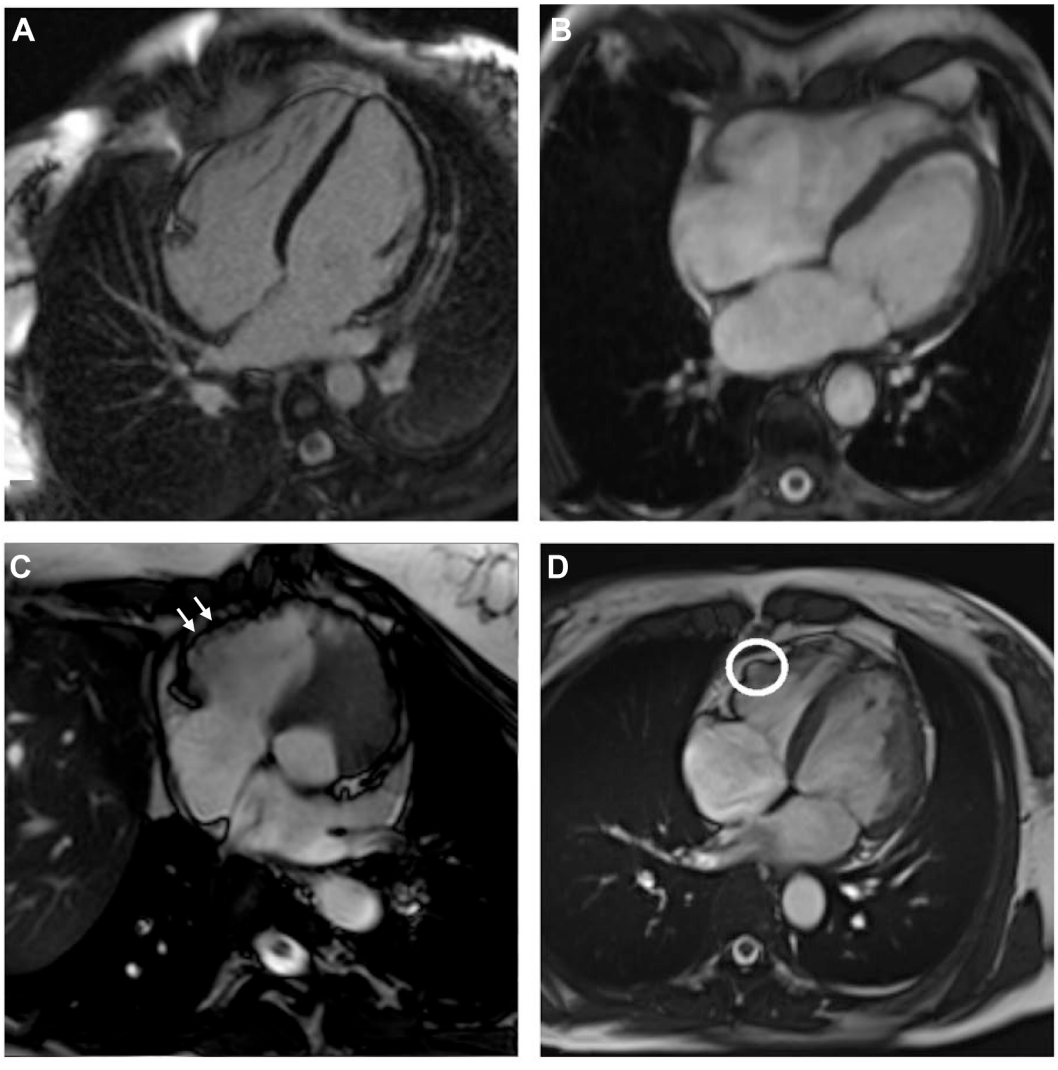
The role of exercise CMR in differentiating physiological cardiac adaptation to exercise from cardiomyopathy has been assessed by a recent study by Claessen et al.[95] These investigators demonstrated that endurance athletes with subepicardial fibrosis, despite having similar resting hemodynamic profiles and exercise capacity to healthy control subjects, exhibited a blunted increase in LVEF during physical stress. Although these findings are intriguing, they remain hypothesis-generating and require validation in larger, prospective cohorts. At present, the clinical utility of exercise CMR in athlete evaluation is limited by the scarcity of robust data, technical complexity, and lack of standardized protocols. As such, its role should be considered exploratory.

OTHER CARDIAC TESTS

Ambulatory ECG monitoring and exercise tests may be useful tools to suggest a pathological phenotype, especially in individuals where first-line tests such as ECG and echocardiogram are abnormal.

AMBULATORY ECG MONITORING. The presence of VAs, such as nonsustained ventricular tachycardia and a high burden of PVBs (typically >500/24 h), are features that may point toward a diagnosis of ACM in the appropriate clinical context.[35] Biffi at al[96] have shown that up to 30% of athletes with ≥2,000 PVBs per 24 hours were found to have underlying structural heart disease. Notably, a high PVB burden has also been associated with an increased risk of VAs and appropriate implantable cardioverter-defibrillator interventions in patients with ACM.[97,98] More recently Gasperetti et al[98] emphasized that arrhythmic risk assessment through Holter monitoring should be considered a dynamic rather than a static process. A progressive increase in PVB burden and the presence of nonsustained ventricular tachycardia during serial

FIGURE 5 **CMR Findings in Athletes and in Patients With ACM**



(A) A 26-year-old active professional male swimmer presenting with occasional light-headedness. Four-chamber steady-state free procession (SSFP) cine view shows harmonic enlargement of the cardiac chambers (indexed left ventricular end-diastolic volume = 121 mL/m^2, indexed RV end-diastolic volume 123 mL/m^2). (B) A 54-year-old woman presenting with palpitations and a high ventricular ectopic burden. A 4-chamber SSFP cine view reveals disproportionate dilation of the RV (indexed left ventricular end-diastolic volume = 65 mL/m^2, indexed RV end-diastolic volume = 156 mL/m^2). Eventually, the patient was diagnosed with ACM and required implantable cardioverter-defibrillator implantation. (C) A 52-year-old man with palpitations and chest pain while running. Four-chamber SSFP cine view shows a crinkling of the RV free wall, also called "accordion sign" (arrows). The patient was eventually diagnosed with ACM. (D) A 47-year-old female swimmer with atypical chest pain. Four-chamber SSFP cine view reveals an aneurysm of the RV free wall (circle). The final diagnosis was ACM. Abbreviations as in Figure 2.

Holter monitoring appear to be strong predictors of sustained VAs within 12 months in patients with ACM.

Recent studies have questioned an approach focused only PVBs burden, and instead emphasized how PVBs morphology, heterogeneity, and complexity, coupling intervals, and relationship to exercise appear to offer a more accurate identification of an underlying cardiac disease. PVBs with a broad RBBB pattern (QRS >130 ms) and superior axis, and PVBs with a broad LBBB pattern and superior axis are uncommon among athletes, and they may be a sign of ACM (Figure 4D). Conversely, fascicular

PVBs, characterized by a typical RBBB, superior QRS axis, and QRS duration <130 ms, and infundibular PVBs, originating from the RVOT or LV outflow tract and commonly characterized by an inferior QRS axis (**Figure 4C**), usually carry a low probability of an underlying disease.[63,64,99]

The use of 12-lead ambulatory monitoring is crucial to assess, not only the burden of PVBs, but also their morphology.

EXERCISE TEST. Exercise tolerance test (ETT) and cardiopulmonary test provide a series of useful information in individuals with a suspected underlying cardiomyopathy. An increase in arrhythmic burden during ETT, with a higher frequency or complexity of PVBs, is uncommon in athletes and points toward a diagnosis of cardiomyopathy, in the appropriate clinical context. Finocchiaro et al[100] specifically highlighted that exercise-induced VAs are frequent among ACM patients (40% of cases), particularly in those with marked biventricular remodeling and LV involvement. Conversely, a reduction of PVBs during physical activity suggests their benign nature.[63,64,99]

Both ETT and cardiopulmonary tests can provide an objective assessment of exercise tolerance, which is typically above the predicted tolerance for age and sex in healthy athletes, and instead reduced in patients with cardiomyopathy.[101]

GENETICS

Pathogenic and likely pathogenic variants in genes encoding for the cardiac desmosomes, including *PKP2*, *DSP*, desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and plakoglobin are found in roughly 60% of patients with ACM.[102,103] Additionally, variants in other genes such as transmembrane protein 43, FLNC, lamin A/C (LMNA), and phospholamban can cause ACM, often with a predominant LV phenotype.[103] ACM cases usually follow an autosomal dominant pattern inheritance, but some genes may rarely be associated with an autosomal recessive pattern (DSC2 and DSG2). In rare cases (1.4%), affected individuals harbor a "de novo" pathogenic variant.

Technological advancements have made it possible to perform rapid, low-cost screening of multiple genes, increasing the accessibility and utilization of genetic testing in clinical practice. Current limitations of genetic testing in ACM include a diagnostic yield with positive results that can be often related to uncertain variants, complicating clinical interpretation.[64] These complexities necessitate a nuanced, multiparametric approach to genetic screening, incorporating phenotypic characteristics and clinical evaluations to optimize its utility and efficacy. Genetic testing could be valuable for confirming diagnoses in individuals displaying a mild phenotype of cardiomyopathy and enabling family cascade screening.[104] It also aids arrhythmic risk stratification by identifying variants linked to highly arrhythmogenic phenotypes, guiding personalized management and prevention.[105] Several studies have highlighted that the impact of exercise on ACM may vary depending on the underlying genetic substrate. Among desmosomal genes, PKP2 has been the most extensively studied, demonstrating that high-intensity exercise accelerates disease onset, increases arrhythmic risk, and worsens structural progression in variant carriers.[18,106] Although data on other genes remain limited, a recent study by Jacobsen et al[107] suggests that the relationship between exercise, VAs, and heart failure progression in individuals with DSP cardiomyopathy is less well defined as no clear correlation has been observed between exercise and adverse outcomes in this population.

FUTURE PERSPECTIVES

Despite growing awareness of the overlap between physiological adaptation in athletes and early signs of ACM, significant uncertainties remain in the field.[35] Artificial intelligence may overcome some of the challenges. A recent study developed a convolutional neural network to analyze 12-lead ECGs, aiming to differentiate ACM from athlete's heart. The negative predictive value in this study was exceptionally high (99.4%),[108] suggesting that artificial intelligence-enhanced ECG analysis could be able to exclude ACM. Nevertheless, further multicenter studies with larger datasets are essential to refine and validate this promising diagnostic approach.

Equally critical is the refinement of exercise prescriptions for gene-positive individuals and patients with borderline phenotypes, with current guidelines providing limited evidence on safe thresholds for physical activity. Future directions include the development of integrated algorithms that merge the expertise of leading centers in

the field with current evidence from the literature. These tools should incorporate genetic variant type, cardiac imaging findings, sport discipline, and individual exercise response to enable a personalized and dynamic approach to exercise prescription.[109]

Another pressing issue lies in the interpretation of genetic findings, particularly variants of uncertain significance, and their role in predicting phenotypic conversion in the context of intense physical training. Systematic variant re-evaluation and the combination of genetic reanalysis with longitudinal clinical data may improve risk stratification and help identify early markers of disease progression in individuals with unresolved genetic findings.[110]

Finally, psychosocial and ethical aspects, such as counseling young athletes, managing family expectations, and the implications of disqualification from sport, require further attention to support holistic patient care.[111]

CONCLUSIONS

Physiological adaptations to long-term exercise in athletes often mimic features seen in ACM, creating substantial challenges in differential diagnosis (**Central Illustration**). ACM is a potentially life-threatening condition, particularly in athletic individuals, where it may manifest as VAs, cardiac arrest, or SCD. Intense physical activity has been shown to accelerate disease expression, especially in genetically predisposed individuals, underscoring the importance of early and accurate diagnosis.

A systematic, multiparametric approach is essential to distinguish benign athletic remodeling from early pathological changes. This includes a thorough personal and family history, expert interpretation of the 12-lead ECG, and the judicious use of advanced imaging modalities such as CMR. In selected cases, genetic testing may provide additional diagnostic clarity and inform risk stratification. Early identification of red flags enables timely intervention, appropriate counselling on exercise participation, and ultimately, improved clinical outcomes.

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