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CONTEMPORARY REVIEW

Exercise Prescription in Arrhythmogenic Cardiomyopathy: Finding the Right Balance Between Risks and Benefits

Lorenzo-Lupo Dei, MD; Jennie Han, MD; Silvio Romano, MD; Luigi Sciarra, MD; Angeliki Asimaki, MsC, PhD; Michael Papadakis, MBBS, MRCP, MD; Sanjay Sharma, BSc, MD; Gherardo Finocchiaro, MD, PhD

ABSTRACT: Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiac condition, often caused by mutations in genes encoding desmosomal proteins. The pathologic hallmark of the disease is a fibrofatty replacement of the myocardium, which constitutes the substrate for potentially fatal ventricular arrhythmias. ACM is one of the most common etiology of sudden cardiac death in athletes and young individuals. Although it is well established that regular exercise confers multiple health benefits and better survival in the general population, intense exercise may accelerate the phenotypic expression and the propensity to ventricular arrhythmias in patients with ACM. This review discusses current evidence regarding the safety and the effects of exercise in ACM. We scrutinize research findings based on animal and human models that raise concerns on the possible detrimental role of intense exercise in this condition. Finally, we examine the current knowledge on exercise prescription focusing on the optimal amount of exercise that should be recommended to patients with ACM.

Key Words: arrhythmogenic cardiomyopathy ■ cardiomyopathies ■ death, sudden, cardiac ■ exercise

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiac condition with a reported prevalence of 1:1000 to 1:5000 in the general population.[1] The pathological hallmark of the disease is a progressive fibrofatty replacement of the myocardium, which constitutes the substrate for potentially fatal ventricular arrhythmias (VAs). ACM is one of the most common causes of sudden cardiac death (SCD) in athletes and young individuals[2] and is generally caused by mutations in genes encoding cardiac desmosomal proteins, although mutations in nondesmosomal genes have also been identified. While initially thought to be a condition affecting the right ventricle only (arrhythmogenic right ventricular [RV] cardiomyopathy), the disease has been increasingly shown to exhibit a biventricular involvement, including isolated left ventricular (LV) involvement in some cases. These observations have resulted in calls for revising the existing diagnostic criteria as well as the nomenclature of the condition, with proposals to use the term *arrhythmogenic cardiomyopathy*.[3]

Studies based on animal and human models suggest that intense exercise may be deleterious, acting as a trigger in exacerbating the phenotype and increasing the propensity for VAs.[4,5] Therefore, a diagnosis of ACM has significant implications in athletes, where the recommendation to abstain from competitive sports has the potential to avoid a detrimental trigger. To add complexity, highly trained athletes may exhibit physiological cardiac changes that overlap with ACM, such as RV dilatation and anterior T-wave inversion at the ECG, resulting in a significant challenge in the differential diagnosis.[6,7]

In this narrative review, we discuss the safety of exercise in ACM and the potential effects on the phenotypic expression of the disease. We appraise current evidence, highlighting strengths and limitations of

Correspondence to: Gherardo Finocchiaro, MD, PhD, FESC, Consultant Cardiologist and Honorary Senior Lecturer St George's Hospital and St George's University of London Cranmer Terrace, London SW17 ORE, UK. Email: gfinocch@sgul.ac.uk

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Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy
SCD	sudden cardiac death
VA	ventricular arrhythmia

studies that have shown a link between exercise and ACM. Finally, we discuss exercise prescription in patients with ACM, an area with many unanswered questions and opportunities for future research.

DIAGNOSIS: AN EVOLVING CONCEPT

In 1982, Marcus et al proposed the term *right ventricular dysplasia* describing 22 patients with sustained ventricular tachycardia (VT) and a structurally abnormal right ventricle.[8] The term *dysplasia* was used because this disease was originally thought to be congenital. In a seminal paper, Thiene et al[9] described the postmortem examination findings of young people with SCD exhibiting RV abnormalities, namely, lipomatous or fibrolipomatous transformation of the RV free wall.

Although the understanding of this condition has improved significantly in the past few decades, diagnosis remains complex and relies on a series of clinical criteria, deriving from personal and family history, genetics, ECG, ambulatory ECG monitoring, imaging, and histopathological findings. The first task force diagnostic criteria were published in 1994, revised in 2010 and in 2020 (international criteria).[10–12] An important development that was captured by the most recent criteria is the recognition of ACM as a biventricular disease.[12]

In this context, cardiac magnetic resonance (CMR) and genetics have become fundamental tools to establish the diagnosis. Imaging with cardiac magnetic resonance (CMR) provides a high level of accuracy in the assessment of chamber volumes, detection of subtle regional wall motion abnormalities, and, most importantly, possible myocardial fibrosis, through tissue characterization after gadolinium administration. The finding of desmosomal pathogenic or likely pathogenic variants in individuals traditionally labeled as affected by dilated cardiomyopathy, contributed to widening the diagnosis in patients who show mainly LV involvement.

ACM AND SUDDEN DEATH IN ATHLETES

ACM is a common cause of SCD in athletes[13–20] (Figure 1). Although data on sedentary individuals are limited, ACM-related SCD appears more prevalent in athletes than in nonathletes.[13,21,22]

A study by Maron et al[14] on 1866 athletes who suffered SCD, found a cardiovascular cause in 1049 (56%). Out of these, 41 (4%) had ACM.[14] Notably, a post-mortem examination was not performed on all decedents. A study by Finocchiaro et al[18] on a large UK autopsy registry, examined 357 athletes who died suddenly between 1994 and 2014 and where the post-mortem examination was performed by specialist cardiac pathologists: 13% of the athletes were diagnosed with ACM.[18]

A study[19] on 202 people with SCD for whom the diagnosis of ACM was made by expert cardiac pathologists showed that death occurred during exercise in 41% of cases. The risk of SCD during exercise was higher in men and in competitive athletes compared with nonathletes.[19] Of note, most decedents with ACM (78%) had no symptoms before SCD. Interestingly, isolated RV disease was observed in only 13% of people with SCD, and the majority (70%) of decedents had biventricular involvement. Petek et al[20] recently examined a cohort of 143 young college athletes who died suddenly between 2002 and 2022. The cause of SCD was identified in 118 of 143 cases, and ACM was diagnosed in 6 athletes (5.1%), with most of them dying during exercise.[20]

ROLE OF INTENSE EXERCISE IN ACM

Regular exercise is beneficial for general and cardiovascular health.[20] However, intense exercise may have a significant impact on the phenotypic expression of ACM and on the propensity to fatal VAs. The link between exercise and ACM has been explored by several studies on human and animal models.

Animal Models

Plakogobin

A seminal study by Kirchhof et al[4] investigated the effects of endurance training on heterozygous plakoglobin-deficient (*JUP*$^{+-}$) mice. An intense swimming protocol of 6 days per week, with duration increased from 5 to 90 minutes per day, over an 8-week training period, exacerbated RV dilatation and RV systolic and diastolic dysfunction and increased the propensity to VAs.[4] Surprisingly, histology and electron microscopy revealed no signs of increased myocardial fibrosis or fibrofatty replacement in the right ventricle of plakoglobin-mutated mice compared with their wild-type exercised littermates. The distribution of desmosomal and adherens junction proteins, as well as connexin 43, was unaltered and reminiscent of controls.[4]

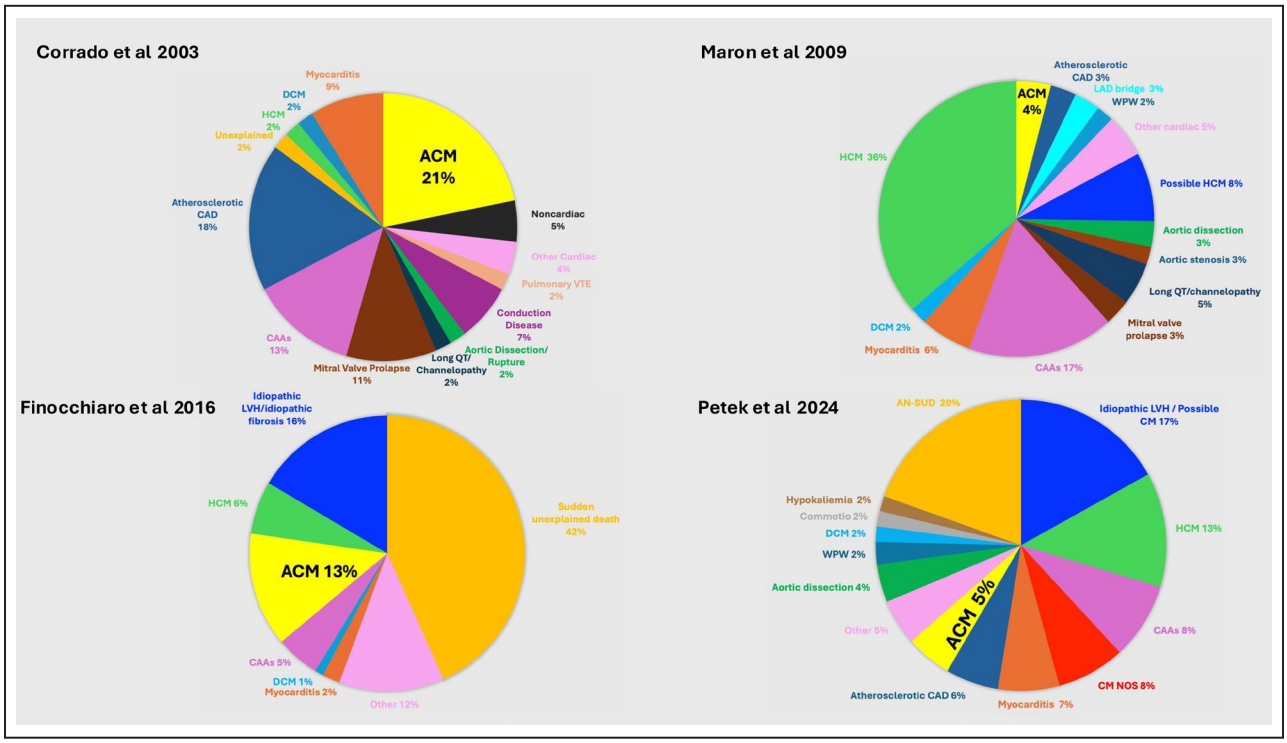

Figure 1. Etiology of sudden death in athletes. Arrhythmogenic cardiomyopathy ranges from 4% to 21% of cases. ACM indicates arrhythmogenic cardiomyopathy; AN-SUD, autopsy-negative sudden unexplained death; CAAs, coronary artery abnormalities; CAD, coronary artery disease; CM, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LAD, left anterior descending artery; LVH, left ventricular hypertrophy; NOS, not otherwise specified; VTE, venous thromboembolism; and WPW, Wolff–Parkinson–White syndrome.

The same group demonstrated that mice with the same variant, when pretreated with load-reducing therapy consisting of furosemide and nitrates before undergoing the exercise protocol, did not develop RV enlargement, and had no increased inducibility of VT. Supposedly, the volume and pressure reduction caused by these medications, reduced RV myocardial stretching and damage.[23]

Plakophillin

Similar results were observed in plakophillin-2 mutated models. Cruz et al[24] evaluated endurance training effect in a mouse model overexpressing a nonsense mutation in the plakophilin-2 (*PKP2*) gene.[24] In this population, sedentary mice showed no ACM phenotype at 6- and 10-month follow-up. In contrast, trained mice, following an 8-week endurance swimming protocol, displayed impaired global RV systolic function and RV regional wall motion abnormalities on cardiac magnetic resonance (CMR) that were consistent with the ACM phenotype. At the histological level, only the mice exposed to intense exercise showed irregular localization and distribution of the main ventricular gap junction protein, connexin 43, suggesting that exercise may result in gap junction remodeling in this model.[24]

Van Opbergen et al[25] confirmed these findings showing that intense exercise in *PKP2* knockout mice was associated with compromised myocyte calcium handling and connexin 43 expression, and a higher susceptibility to cardiac arrhythmias due to slowed conduction velocity.[25] Moncayo-Arlandi et al,[26] in a truncated *PKP2* mouse model, subjected to intense exercise, found exercise to be associated with macroscopic alterations such as RV dilation and dysfunction and ruptures of intercalated discs.[26]

Desmoplakin

A study by Lyon et al[27] on desmoplakin knockout mice investigated whether SCD was influenced by exercise and catecholamine stimulation in this specific model. The protocol consisted of running on a treadmill for 1 session of at least 45 minutes or until exhaustion. Subsequently, mice received a high (2 mg/kg) or low (0.5 mg/kg) epinephrine dose. The low dose caused a higher number of premature ventricular beats in desmoplakin knockout mice when compared with healthy littermates, the high dose induced SCD in 20% of the mutated mice group, a phenomenon that was not observed in littermate controls. This study suggested that epinephrine on top of vigorous exercise could induce

fatal sudden arrhythmias in the predisposed heart of desmoplakin knockout mice.[27]

To further investigate the desmoplakin mutation-related phenotype, Martherus et al[28] evaluated the effects of endurance exercise in ACM by comparing transgenic mice overexpressing the human cardiac-specific desmoplakin isoform, wild-type, or mutant R2834H mice. Mice were exposed to a treadmill involuntary running protocol gradually increasing speed, distance and inclination. After 12 weeks of exercise, mutant R2834H mice showed significant RV dilatation and wall thinning compared with isoform, wild-type controls. This specific model showed no LV dilatation or dysfunction, but missense desmoplakin mutations notably cause a LV variant of the disease.[29]

Interestingly, a study on myocyte-specific desmoplakin haplo-insufficient mice[30] showed that an intense 60-minute daily treadmill running protocol, with a gradual increase in slope and speed over 3 months, may benefit cardiomyocytes in ACM. This regimen restored dysregulated gene transcription, reduced apoptosis, and induced eccentric cardiac hypertrophy without affecting systolic function or increasing arrhythmia susceptibility. The gradually incremented workload of the intense exercise protocol may explain the absence of a deleterious effect.[30]

Desmoglein-2

Chelko et al[31,32] evaluated the effect of intense exercise on a mice population harboring a knock-in mutation in the *DSG2* gene that causes the loss of exons 4 and 5 and creates 2 stop codons in exon 6, leading to mRNA degradation through the nonsense-mediated decay process. This resulted in the absence of desmoglein at the intercellular junction as proven by Western analysis and immunostaining.

Interestingly, heterozygous *DSG2*$^{mut/+}$ mice did not exhibit ACM phenotype at rest. However, when exposed to chronic physical exertion, consisting of an 11-week endurance swim protocol (10 minutes per day increment, 5 days per week, up to a maximum of 90 minutes a day from 5 weeks of age to 16 weeks of age), they developed cardiac abnormalities such as myocardial fibrosis and inflammation, and intercalated disc protein redistribution. This suggests that intense physical activity exacerbates the disease in this model.[31]

Conversely, sedentary homozygous mutated mice (*DSG2*$^{mut/mut}$) exhibited key ACM phenotypes by early adulthood (16 weeks of age), including ECG repolarization and depolarization abnormalities, RV and LV dysfunction, intercalated disc remodeling, and myocyte inflammation and fibrosis, as well as improper handling of cardiac calcium and myocardial lipid accumulation.[31,32]

Despite these abnormalities, sedentary *DSG2*$^{mut/mut}$ mice could live well into adulthood. However, the same exercise protocol resulted in an increasing number of exercise-related sudden deaths, when compared with *DSG2*$^{mut/+}$ and wild-type mice, proving a clear correlation between physical activity and fatal outcomes in this population.[31]

Effects of Intense Exercise on the Myocardium of Healthy Rats

Benito et al[33] investigated the effect of exercise on the healthy myocardium of non–genetically mutated rats. Investigators randomly assigned rats to sedentary or intensive exercise groups. Intensive exercise rats underwent a steady-state running protocol for 60 minutes, 5 days a week, for up to a 16-week period. The intensive exercise rats showed a decline in diastolic biventricular function and higher VA inducibility during programmed stimulation at the end of the intensive exercise training period. After heart explant, structural changes such as myocardial fibrosis but no fibrofatty replacement were observed. An additional series of rats underwent the training protocol followed by discontinuation of exercise to assess the reversibility of exercise-induced myocardial remodeling (hypertrophy, dilatation, fibrosis). Myocardial fibrosis, hypertrophy and dilation of the RV of discontinuation-of-exercise rats progressively reduced during the sedentary period. These data suggest that in the healthy myocardium of rats, the changes induced by vigorous training are reversible after cessation of exercise.[33]

In summary, recent studies suggest that intense exercise can exacerbate RV or biventricular dilatation, dysfunction, and VAs both in desmosome gene mutated and in the healthy myocardium of rodents (Figure 2). Apparently, in nonmutated rats, the myocardial alterations are reversible with the interruption of intense physical activity. However, at least in some models, these changes are not associated with some microscopic alterations typical of ACM such as fibrofatty replacement.

Human Studies

Studies on the effects of exercise in patients with ACM or in individuals harboring pathogenic or likely pathogenic variants are generally retrospective and often based on patients' self-assessment of exercise activities before the diagnosis (Figure 3).

The first report quantitating the impact of sports on ACM is from Corrado et al.[13] These authors showed that young individuals engaging in competitive sports had a 2.5-fold higher relative risk of SCD compared with sedentary individuals. In the same study, on a large cohort of SCDs in young individuals, the leading cause was ACM (21% of the cases). The authors concluded that intense exercise may act as a trigger

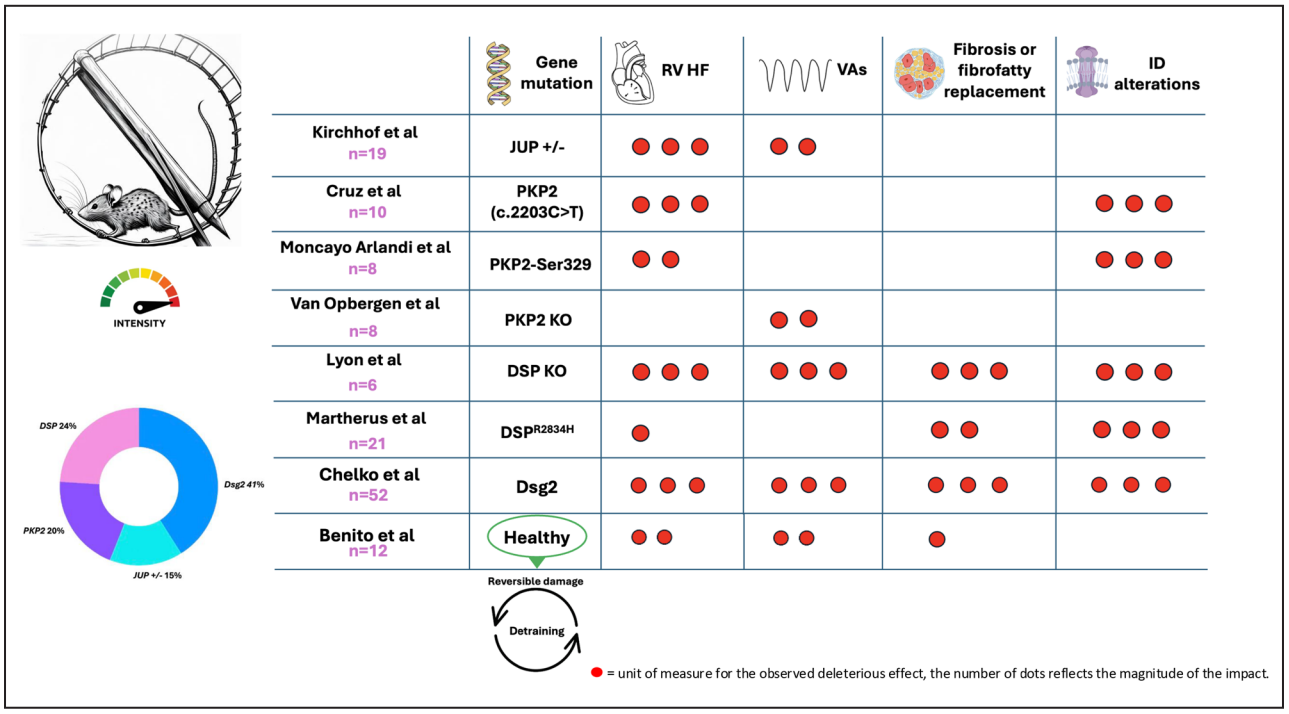

Figure 2. Animal models of intense exercise in ACM. Intense exercise has shown to induce different modifications depending on the phenotype.
ACM indicates arrhythmogenic cardiomyopathy; *DSP*, desmoplakia (gene); ID, intercalated discs; *JUP*, junction plakoglobin (gene); *PKP2*, plakophilin 2 (gene); RV HF, right ventricular heart failure; and VAs, ventricular arrhythmias.

for fatal VAs in individuals with an underlying cardiac condition, particularly in ACM.

Following the aforementioned evidence on animal models, a possible direct effect of intense exercise on the phenotype of ACM has been recently tested on patients. James et al[5] explored the influence of exercise on age-related penetrance and arrhythmic risk in a cohort of 87 desmosomal mutation carriers (*PKP2*, 87%; *DSG*, 8%; *DSP*, 4%; *DSC2*, 1%). Exercise history was evaluated through structured interviews at the time of diagnosis. Endurance athletes were more likely to meet the revised task force diagnostic criteria for arrhythmogenic RV cardiomyopathy (ARVC), to have VAs, and to have heart failure symptoms at a younger age, compared with sedentary individuals. Notably, patients who exercised less after diagnosis had a lower risk of VT/ventricular fibrillation compared with those who continued to exercise to the same levels.[5] This reinforced the idea that the ACM phenotype might be a continuum shaped by the interaction of genetics and the environment (exercise).

To corroborate the hypothesis of a strong effect of intense exercise on ACM phenotype, Saberniak et al[34] evaluated a larger European cohort of 110 patients (91% *PKP2* mutation positive) who either met the revised task force diagnostic criteria or were genotype-positive family members of a proband. This study showed that athletes (>4 hours per week of strenuous exercise for >6 years) exhibited more commonly impaired biventricular systolic function and earlier onset of VAs and had a higher risk to undergo cardiac transplantation, compared with sedentary patients and family members harboring a desmosomal mutation.

The safety of American Heart Association–recommended minimum exercise levels has been demonstrated in unaffected *PKP2* mutation carriers, in whom adherence to these guidelines was significantly associated with a lower risk of phenotype progression and VAs.[35,36]

Similar findings were reported in a cohort of 108 probands[37] with ACM. Individuals who engaged in competitive sports before the diagnosis had a 2-fold increased likelihood of developing VT and death during follow-up. No significant difference in risk of VT/death emerged between sedentary patients and those who participated in recreational sports.[37]

A retrospective study by Lie et al,[38] in a population of 173 consecutive patients with ACM (*PKP2*, 64%; *DSP*, 5%; *DSG2*, 4%; *DSC2*, 1%; G–, 26%), showed that VAs were more common in patients who had previously engaged in high-intensity exercise compared with those participating in low-intensity exercise. The combination of high-intensity and long-duration exercise, along with male sex, was associated with the highest risk. However, low-intensity exercise, even of long duration, was associated with a milder phenotype. A recent study from the same group[39] prospectively showed that high-intensity

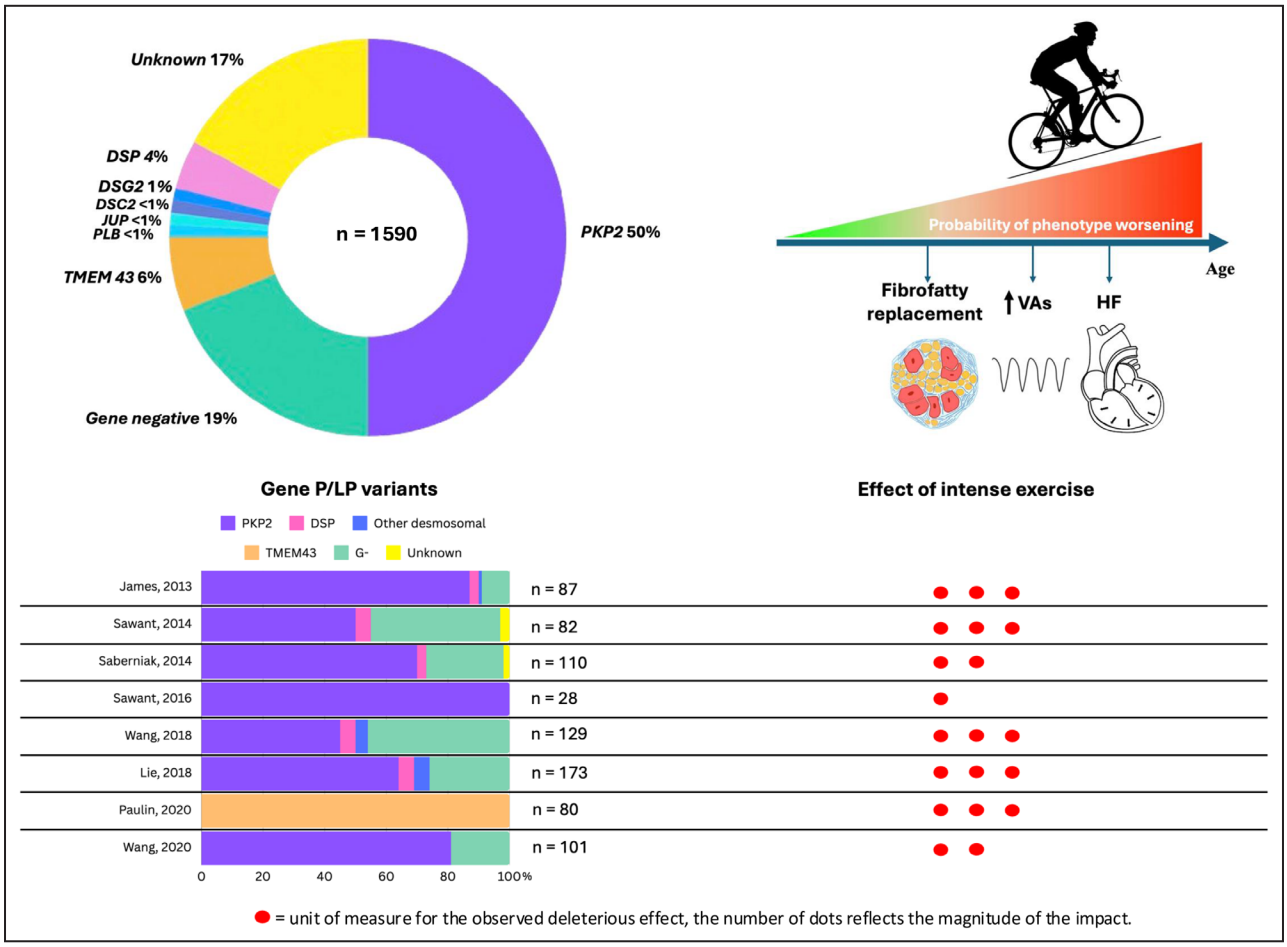

Figure 3. Human studies. The likelihood of phenotype worsening increases with the intensity of exercise. Total number of patients (n=1590) refers to all the studies evaluated in this review. On the bottom part of the figure, we selected[8] studies that included a relatively high number of patients with high proportion of pathogenic or likely pathogenic variants.
DSC2 indicates desmocollin 2 (gene); *DSG2*, desmoglein 2 (gene); *DSP*, desmoplakin (gene); G–, gene negative; *JUP*, junction plakoglobin (gene); *PLB*, pbosphalamban (gene); *PKP2*, plakophilin 2 (gene); *TMEM43*, transmembrane protein 43 (gene); and VAs, ventricular arrhythmias.

physical activity, along with T-wave inversion in V3 and increased LV mechanical dispersion (assessed by echo-longitudinal strain), were robust predictors of VAs.

These data have also been confirmed in the pediatric population. Te Riele et al[40] showed that patients who displayed overt manifestations of the disease at a young age (<18 years) had previously engaged in endurance sports in high proportion.[40] This finding suggests that the pediatric age is a vulnerable period, highlighting the need to evaluate individuals at risk of developing an overt phenotype and to manage physical activity accordingly. This is especially significant, as pediatric onset is more often associated with SCD or cardiac arrest.[40] Minimum exercise levels appear to be safe for unaffected PKP2 mutation carriers, according to the American Heart Association's recommendations. Adherence to these guidelines was significantly associated with a lower risk of phenotype progression and ventricular arrhythmias (VAs).

ACM Caused by Intense Exercise?

To reinforce the concept of a possible deleterious effect of exercise on ACM, Heidbüchel et al[41] proposed a novel perspective on the disease, suggesting that intense exercise can cause the development of an ACM phenotype. These authors observed a recurring pattern of mild RV systolic dysfunction and malignant VAs in professional cyclists who presented with palpitations but had no family history of cardiomyopathy. Most of these cyclists met the diagnostic criteria for the disease. A minority (12.8%) of athletes fulfilling diagnostic criteria harbored a predisposing genetic mutation, as shown by La Gerche et al in a subsequent study.[42] These findings corroborate the hypothesis that the ACM phenotype may be caused by intense exercise in individuals who are gene elusive and where indeed an environmental factor may be the main trigger of pathological cardiac manifestations.

Engaging with the same hypothesis, Sawant et al[43] focused on gene-elusive patients and found that all the studied individuals who displayed an overt phenotype of the disease were athletes engaging in intense exercise, and a minority reported a family history of cardiomyopathy.[43]

Exercise in Patients With an Implantable Cardioverter-Defibrillator

Few studies assessed how continuing intense exercise affects the risk of developing VAs, in patients with ACM implanted with an implantable cardioverter-defibrillator (ICD). Wang et al[44] interviewed 129 patients with ACM (*PKP2*, 45%; *DSP*, 5%; *DSG*, 1%; *DSC*, 1%; *JUP*, 1%; *PLB*, 1%; digenic, 5%; genotype negative, 41%) who had received an ICD ≈4.2 years prior (36% for primary prevention). Exercise dose (metabolic equivalent task-hours) was investigated before and after diagnosis. Individuals who reduced the exercise dose after clinical presentation were less likely to develop VAs treated by the device. Among previously athletic individuals who significantly reduced their exercise activity, the risk of arrhythmias remained high. This suggests that reducing exercise alone is unlikely to be sufficient in influencing the decision to implant an ICD.[44]

A multinational registry composed of 372 athletes with an ICD, of which 53 (14%) had ACM, showed no SCDs during or immediately after sports participation. However, an underlying diagnosis of ACM was associated with an increased risk of exercise-induced ICD-appropriate shocks.[45]

In summary, studies on patients with ACM appear to support a mechanistic link between intense exercise and phenotypic expression of the disease. However, there are common limitations that mitigate the clinical significance of these results. The mostly retrospective nature of the studies, lack of randomized controlled trials, potential bias in self-reported exercise history, and the limited sample size may impact the generalizability of these findings. Most of the cohorts were composed of individuals harboring pathogenic or likely pathogenic variants in desmosomal genes, with patients carrying *PKP2* mutations being the most studied. This may limit the applicability of the results to a broader ACM population, considering the extreme heterogeneity of the condition from a genetic and phenotypic standpoint. Additionally, most data are derived from tertiary care centers, potentially introducing a selection bias.

HEALTH BENEFITS OF EXERCISE

Regular exercise is widely recognized as a cornerstone for reducing cardiovascular risk in the general population and patients with cardiovascular disease.[46,47]

Several studies have demonstrated lower all-cause death and reduced incidence of cardiovascular diseases,[48,49] cancer,[50,51] and metabolic conditions[52] in individuals who engage in regular exercise. Physical activity decreases the burden of cardiovascular risk factors, including hypertension,[53,54] diabetes, and hypercholesterolemia.[52] An active lifestyle is therefore strongly advocated by the World Health Organization and international guidelines for primary and secondary prevention of cardiovascular disease. The European Society of Cardiology guidelines recommend a minimum of 150 minutes per week of moderate-intensity aerobic activity.[46] Exercise has been observed to have a "dose-dependent" effect on cardiovascular health outcomes, and those who undertake larger volumes of regular exercise achieve greater benefits.[46] Very high volumes of exercise may reduce the health benefits or lead to a worse outcome (U-shaped relationship between exercise volume and outcomes).[55] A sedentary lifestyle is considered a major contributor to global health burdens,[56] obesity, and coronary artery disease.[57]

EXERCISE PRESCRIPTION IN PATIENTS WITH ACM

Given the premise that regular exercise provides a wide range of health benefits, it would be reasonable to think that patients with ACM should also be encouraged to practice an active lifestyle. However, in practical terms, this perception is often mitigated by concerns derived from the evidence supporting a deleterious impact of exercise in ACM. International guidelines embrace a cautious approach in recommending regular exercise in these patients. The European Society of Cardiology guidelines on cardiomyopathies[58] support engagement in 150 minutes of low-intensity exercise per week, which should also be encouraged in patients with ACM. Low and moderate-intensity recreational exercise is considered a safe option in patients with a mild phenotypic expression from an electrical and structural standpoint. The same guidelines[58] discourage high-intensity exercise and competitive sports for individuals with ACM including individuals who are genotype positive/phenotype negative. International recommendations[58] are often based on consensus (level of evidence C) due to the lack of robust evidence on this matter (Table 1).

Exercise prescription in patients with cardiomyopathy is challenging, as cardiomyopathy specialists may have limited experience in exercise prescription, while sports medicine specialists may feel uncomfortable managing these patients. It is our group opinion that exercise prescription for patients with ACM should be conducted within specialized centers. In our

Table 1. Current AHA and ESC Recommendations for Sport Participation in ACM in Overt Phenotype and Genotype-Positive/Phenotype-Negative Patients

	2015 AHA/ACC scientific statement	2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease	2022 ESC guidelines of VA and prevention of SCD	2023 ESC guidelines on cardiomyopathies
Definite diagnosis	Athletes with a definite diagnosis of ARVC should not participate in most competitive sports, with the possible exception of low-intensity class 1A sports. (III C) Athletes with a borderline diagnosis of ARVC should not participate in most competitive sports, with the possible exception of low-intensity class 1A sports. (III C) Athletes with a possible diagnosis of ARVC (genotype-positive, phenotype-negative individuals only show 1 major criterion, formally belonging to this category) should not participate in most competitive sports, with the possible exception of low-intensity class 1A sports. (III C)	All individuals can be considered for low-intensity exercise. (IIa C) Patients who have risk markers may participate in low- or moderate-intensity recreational exercise depending on individualized expert assessment. (IIb C) High-intensity exercise and competitive sports are not recommended. (III B) Participation in high-intensity recreational exercise/sports or any competitive sports is not recommended. (III B) Annual assessment should be considered for phenotypic features and risk stratification purposes. (IIa C)	Avoidance of high-intensity exercise is recommended in patients with a definite diagnosis of ARVC. (I B) Avoidance of high-intensity exercise may be considered in carriers of ACM- related pathogenic mutations and no phenotype. (IIb C)	Regular low- to moderate-intensity exercise is recommended in all able individuals with cardiomyopathy (all cardiomyopathies). (I C) Moderate- and high-intensity exercise, including competitive sport, is not recommended in individuals with ARVC. (III B)
Genotype positive/ phenotype negative	Athletes with a possible diagnosis of ARVC (genotype-positive, phenotype-negative individuals only show 1 major criterion, formally belonging to this category) should not participate in most competitive sports, with the possible exception of low-intensity class 1A sports. (III C)	Participation in high-intensity recreational exercise/sports or any competitive sports is not recommended. (III B) Annual assessment should be considered for phenotypic features and risk stratification purposes. (IIa C)	Avoidance of high-intensity exercise may be considered in carriers of ARVC-related pathogenic mutations and no phenotype. (IIb C)	Avoidance of high-intensity exercise, including competitive sport, may be considered in genotype-positive/phenotype-negative individuals in families with ARVC. (IIb C)

ACM indicates arrhythmogenic cardiomyopathy; AHA/ACC, American Heart Association/American College of Cardiology; ARVC, arrhythmogenic right ventricular cardiomyopathy; ESC, European Society of Cardiology; SCD, sudden cardiac death; and VA, ventricular arrhythmias.

experience, an interdisciplinary approach, which is inclusive of a wide range of professional figures, from exercise physiologists to sports medicine, cardiomyopathy, imaging, and electrophysiology specialists, integrating cardiac rehabilitation programs is the most effective way to provide holistic care that is focused on the individual patient.

It is our group practice to embrace a shared-decision approach, which takes into account the risks and benefits of regular exercise, contextualized to the individual affected. This includes patients' preferences in terms of type of sport. The many knowledge gaps in the field are always openly described to patients.

Intensity of exercise is generally classified according to ventilatory thresholds, VO_2Max (the maximum amount of oxygen the mitochondria can consume at peak exertion to produce adenosine triphosphate), and maximum heart rate measured at cardiopulmonary exercise test (Table 2). Cardiopulmonary exercise testing is the first step to identify ventilatory thresholds, which are crucial for determining individualized exercise intensity,[59] and is a useful test in tailoring exercise prescription in patients with cardiovascular disease, also revealing possible exercise-induced arrhythmias.[60] The interval between ventilatory threshold 1 and ventilatory threshold 2 identifies what moderate levels of exercise for the individual patient are. Knowledge of the patient's heart rate at ventilatory threshold 1 and ventilatory threshold 2 is relevant information for self-directed exercise, which may be aided by the use of wearable devices to monitor the heart rate. As far as static exercise is concerned, since the chronotropic response may be less than in dynamic exercise for the same levels of oxygen consumption, the authors consider it is advisable to limit upper and lower limb loading to no more than 20% and 50% of body weight, respectively, and to avoid exceeding 6 repetitions.[61]

Table 2. Indices of Exercise Intensity

	Vo_2 max (%)	HR max (%)	HRR (%)
Low-intensity physical exercise	<40	<55	<40
Moderate-intensity physical exercise	40–69	55–74	40–69
High-intensity physical exercise	70–85	75–90	70–85
Very high-intensity physical exercise	>85	>90	>85

HR max indicates maximum heart rate; HRR, heart rate reserve (calculated by subtracting the resting heart rate from the maximum heart rate); and Vo_2 max, the maximum amount of oxygen that muscle's mitochondria can consume at peak exertion to produce adenosine-triphosphate (aerobic metabolism).

Although the cardiopulmonary exercise test may clarify the levels of exercise intensity, helping to identify safe thresholds for moderate exercise, the impact of the duration of exercise at a certain intensity is poorly understood. A study by Lie et al[38] showed that exercise intensity appears to have a deeper impact on outcomes than the duration of exercise. Exercise sustained for long periods, but of low intensity appears to be associated with a milder phenotype.

It is the authors' opinion that certain recommendations should be part of the consultation with every patient with cardiomyopathy who wishes to exercise regularly. These include avoiding exercise in extreme adverse environmental conditions, exercise programs that involve regular training with increasing workloads focused on achieving high levels of conditioning and excellence, and intensive static isometric exertion. Some patients may experience disease flare-ups that manifest as hot phases of detectable myocarditis or as an intensification of arrhythmic events. These events increase the arrhythmic risk, and intense exercise should be discouraged for at least 3 to 6 months. Reassessment of risk should be conducted before restarting exercise activity.[46]

Sports disqualification is a sensitive issue in children and adolescents, where sports activities facilitate socialization. Children with ACM are more likely to present with sudden cardiac arrest,[40] justifying careful risk assessment. While strenuous sports should be avoided, even in genotype-positive/phenotype-negative children,[36,62] participation in noncompetitive school activities may be considered.

Genotype knowledge is crucial, as some genes, like *PKP2*, confer vulnerability to high-intensity exercise. Less is known about those linked to both dilated cardiomyopathy and ACM. While *LMNA* variants may worsen outcomes with intense exercise,[62] effects on other genetic backgrounds remain unclear. A cautious, individualized exercise approach is warranted. In specific patients, it should be accepted that low-intensity exercise is the only permissible activity when VAs are exercise induced or when heart failure symptoms are limiting factors.

Some patients may experience disease flare-ups that manifest as hot phases of detectable myocarditis or as an intensification of arrhythmic events. These events increase the arrhythmic risk, and intense exercise should be discouraged for at least 3 to 6 months.

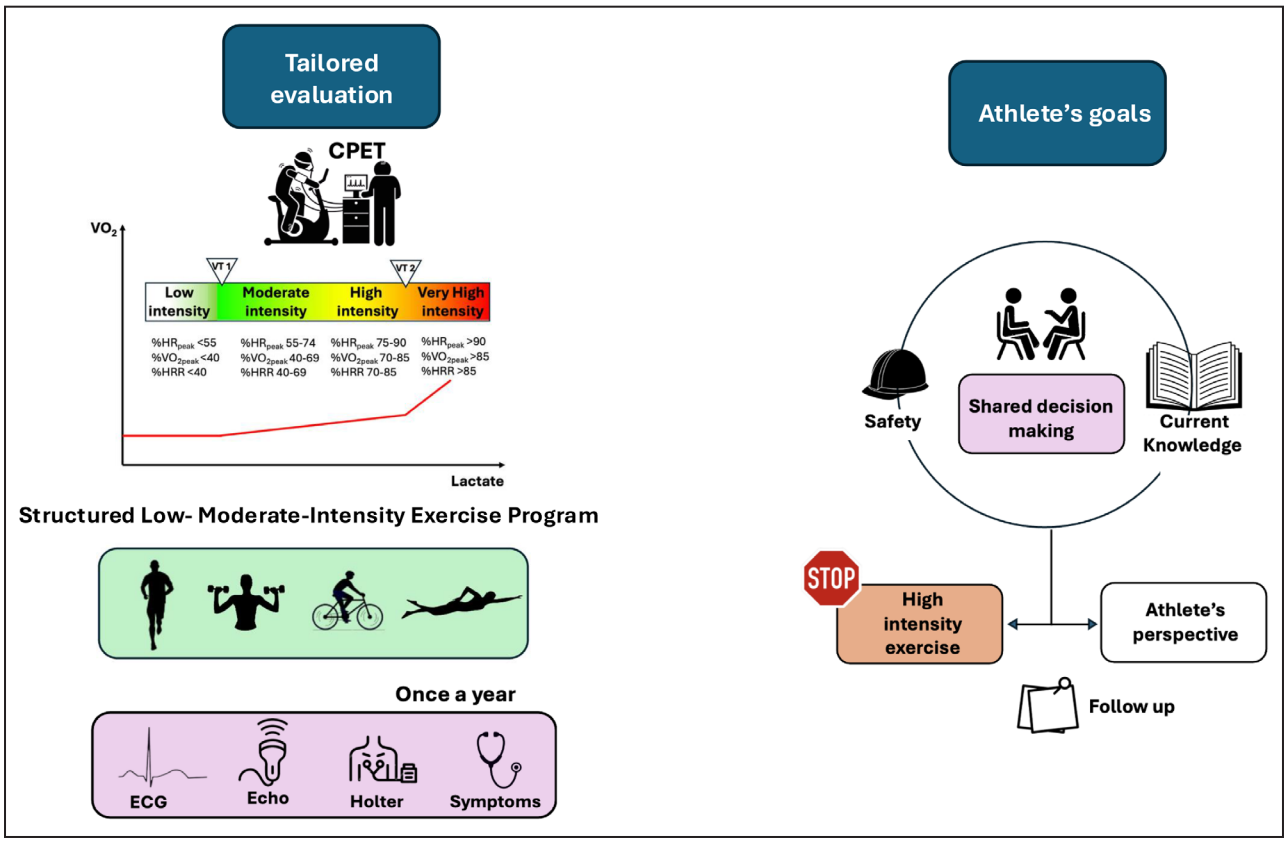

Figure 4. Exercise prescription in arrhythmogenic cardiomyopathy: tailored evaluation and safe low-to-moderate intensity exercise plan with annual follow-up; shared decision making for athletes, balancing safety and individual preferences.
ACM indicates arrhythmogenic cardiomyopathy; CRF, cardiovascular risk factors; HRpeak, heart rate at peak exercise; HRR peak, heart rate reserve at peak exercise; VAs, ventricular arrhythmias; and Vo_2peak, peak oxygen consumption.

Reassessment of risk should be conducted before restarting exercise activity.

Considering the evolving nature of the disease, undergoing regular follow-up to monitor possible disease progression in patients with ACM who wish to continue to exercise, is crucial (Figure 4). Cardiac investigations aimed at monitoring the effects of exercise on the phenotype from a structural and electrical standpoint (echocardiogram, ECG, and ambulatory monitoring) and cardiopulmonary exercise test to assess cardiovascular fitness and propensity to arrhythmias during exercise are warranted.

LIMITATIONS OF CURRENT EVIDENCE

The evidence obtained from animal models may not be fully applicable to human models. These studies focused on specific mutations, limiting the applicability of the results to the human cohorts, often characterized by a significant variability in terms of genetic background. Moreover, the exercise intensity achievable in experimental models may not accurately replicate the training regimens of humans, including athletes.

Current evidence on human studies shares common limitations, including their retrospective nature, reliance on self-reported exercise assessments, and the potential for gaps in ascertaining a "phenotype-negative" status. Moreover, the definition and nomenclature of the disease has changed significantly during the past decades, as technology advances have enabled us to diagnose this condition more precisely, capturing the wider spectrum of manifestations.

Our understanding of the impact of exercise on individuals with ACM is based on studies focusing on patient groups with variants in the same gene. Often, evidence is derived from subgroups of patients with specific gene mutations, mostly in the *PKP2* gene, and rarely in others such as *DSP*, *DSG*, and *TMEM43*.[63] However, these results are generalized to the wider spectrum of the disease. The lack of knowledge on the safety and effect of moderate exercise is fulfilled by consensus-based recommendations.

FUTURE PERSPECTIVES

Building upon the existing knowledge, randomized clinical trials are needed to address knowledge gaps on the impact of intensive exercise in individuals with cardiovascular diseases and to determine the optimal and safe exercise doses for patients with ACM. Moreover, further research is needed to clarify the threshold for a safe exercise recommendation.

A deeper understanding of the complex interplay between genotype, epigenetic, and environmental factors may enhance our understanding of the disease, also as far as lifestyle recommendations are concerned.

CONCLUSIONS

ACM is a common cause of SCD in athletes and young individuals.[2] A link between intense exercise, clinical expression, and risk of potentially fatal arrhythmias has been shown by several studies. Both animal and human models suggest that intense exercise may accelerate disease progression (even in individuals who are genotype positive/phenotype negative), increasing the risk of VAs that can lead to SCD. In view of the above, there is consensus that patients with ACM should be advised against high-intensity and competitive sports. The evidence on this subject is limited to specific genotypes and is based mainly on retrospective studies. A generalization to the whole spectrum of ACM is probably the safest approach, waiting for further studies aimed at capturing the wide heterogeneity of this condition. Although it appears reasonable not to deny patients with ACM the numerous health benefits associated with low- to moderate-intensity exercise, the evidence on the safety and possible effects on the progression of the disease is lacking. Exercise recommendations should be individually prescribed by professionals who are experienced in the management of this condition in centers of excellence that can tackle the many complexities in terms of diagnosis and clinical management.

ARTICLE INFORMATION

Affiliations

Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy (L-L.D., S.R., L.S.); Cardiovascular Sciences Research Centre, St George's, University of London, UK (L-L.D., A.A., M.P., S.S., G.F.); and St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK (J.H.).

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