REVIEW

# Arrhythmogenic cardiomyopathy and sports: from mice to humans

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## INTRODUCTION

Since its clinical description in 1982[1], arrhythmogenic cardiomyopathy (AC) has been recognized as an important cause of sudden cardiac death (SCD) in young adults, especially in association with athletic activity[2]. Young adults engaging in competitive sports have an increased risk of SCD although sport is not the cause of cardiac arrest but rather acts as a trigger in the presence of an underlying heart disease predisposing to life-threatening ventricular arrhythmias (VA)[3].

AC is an inheritable heart disease predominantly caused by mutation of genes encoding cardiac desmosomes, proteins responsible of connection between cardiac myocytes[4]. Under increased wall stress, dysfunctional desmosomes are unable to maintain cellular adhesion resulting in cell detachment, abnormal cell-to-cell signaling and finally apoptosis. Death myocytes are replaced by fibro fatty tissue and the fibro-fatty scar becomes a substrate for life-threatening VA and SCD often in young individuals[5]. Progressive myocardial atrophy leads to aneurysmal formation, ventricular dilatation and dysfunction. The disproportionate load imposed by exercise on the right ventricle (RV) thinner wall has been proposed as an explanation for the negative effects of strenuous physical activity in a disorder that predominantly affects the RV[6].

## EFFECTS OF EXERCISE IN ARRHYTHMOGENIC CARDIOMYOPATHY

The hypothesis that AC phenotype is accelerated by strenuous training was first studied in mice[7]. Heterozygous deletion of plakoglobin led to accelerated development of RV enlargement, dysfunction and arrhythmias in mice[7].

First, clinical studies on desmosomal mutation carriers confirmed the influence of exercise on the outcome of patients with AC suggesting that exercise may be a trigger of phenotypical penetrance[8]. Both in probands and in asymptomatic mutation positive family members, athletic activity increases risk of life threatening arrhythmic events and biventricular myocardial dysfunction; furthermore, exercise accelerates onset of symptoms and life threatening VA[9].

## PHYSICAL ACTIVITY RECOMMENDATIONS

Therefore it seemed reasonably to recommend competitive sports restriction in AC patients and mutation carriers family members, except for low intensity sports like archery, bowling, cricket, golf and rifle shooting[10]. As SCD from AC may occur unexpectedly in healthy asymptomatic young people, especially athletes, implementation of screening programs in athletes has been proposed but are controversial. Indeed, preparticipation screening program in young competitive athletes led to a decline in fatal events and in a concomitant increase of number of athletes successfully diagnosed and disqualified from competition, the greatest decline being noticed in death rates from AC[11].

Instead, physicians are often confronted with dilemma of making recommendation for patients who want to have physically active lifestyles by participating in recreational and leisure-time activities. When compared to sedentary patients, recreational exercise was not associated with the same deleterious effects as competitive sports in AC probands[12]. A dose-dependent relationship between athletic history and phenotypic severity is supported by a recent study that found that PKP2 mutation positive family mem-

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bers who limited exercise dose to the upper bound for what is recommended for healthy life style[13] were less likely to develop AC diagnosis and arrhythmias[14]. The positive relationship between exercise amount and outcome of patients with AC has been recently meticulously explored[15]. It have been shown that prevalence of VA and degree of structural alterations is directly proportional with exercise dose and that outcome in AC patients is more dependent on exercise intensity than exercise duration[15]. Although these finding could be used to make further recommendations, the safety of low-intensity exercise remains to be determined.

For now, there is no definite recommendations regarding recreational physical activity for AC patients; consensus documents states that clinicians should individualize exercise prescription according to the clinical status[10].

Probands[12] and mutation carriers individuals[8] who continue to exercise competitively after AC diagnosis have an adverse arrhythmic outcome. Furthermore, following first life threatening arrhythmic event, reducing exercise level from competitive to either recreational or inactive didn't protect against future arrhythmic events as the absolute risk of ventricular arrhythmias and SCD remains high in AC independent of physical activity, but still decreased the rate of arrhythmias during follow-up[12]. Nevertheless, the impact of exercise restriction on non-arrhythmic outcome and development of full AC phenotype has never been studied.

## MUTATION NEGATIVE ARRHYTHMOGENIC CARDIOMYOPATHY

It has been hypothesized that in „gene elusive" patients, greater exercise dose can be sufficient to cause AC phenotype. This theory has been supported by studies that found lower prevalence of familial disease and desmosomal mutations in athletic cohorts[16,17]. Although strenuous exercise has a clear environmental role on AC development, the impact of genetic determinism on disease penetrance and expression cannot be excluded as some „gene-elusive" patients has clear familial history and only a small proportion of athletes are susceptible[17]. „Gene-elusive" AC phenotype can also be caused by mutations in unknown genes or by low penetrant variants of desmosomal and other genes[17].

The hypothesis of disproportional exercise-induced RV remodeling[18] as a substrate for arrhythmias has been explored both in experimental[19] and in clinical studies[20]. It has been proposed that a continuum from genetically inherited AC in which dysfunctional desmosomes can be prone to spontaneous rupture to exercise-induced AC phenotype in which extreme doses of exercise can disrupt even normal desmosomes in the vulnerable host exists[21]. If intact desmosomes can be damaged by high RV wall stress in the absence of any genetic predisposition is still questionable.

## DIFFERENTIATING ATHLETE´S HEART FROM RIGHT HEART CARDIOMYOPATHY

History of exposure to competitive physical activity has physiologic cardiac effects known as „athlete´s heart"[22] that sometimes can be confounded with cardiac pathological states. Endurance training promotes RV dilatation with consistent increase of the RV inflow and outflow segments. According to 2010 Revised Task Force criteria[23], AC diagnosis is only fulfilled when dimensional criteria are accompanied by regional wall motion abnormalities. Nevertheless it has been proposed to use only major indexed dimensional criteria to define RV enlargement compatible with AC in athletes[24]. There are some other imaging criteria that may help in differential diagnosis between AC and physiologic RV adaptation. In AC patients we often observe predominant increase of the RV outflow tract, a ratio of RV inflow dimension/left ventricle (LV) dimension >0.9 on echocardiography, regional akinesia/dyskinesia, aneurysmal deformation and global systolic RV dysfunction[25] (RV fractional area change ≤40% and RV longitudinal strain of the lateral RV free wall worse than -23 [26]).

Furthermore, integrating clinical finding in the decision algorithm can be of great help. Family history of SCD/AC, anterior T wave inversion on ECG, VA with left bundle branch block (LBBB) morphology and exercise induced ventricular tachycardia are additional arguments for AC[25].

Whenever AC is suspected, clinician should ask the patient about exercise habits in order to make a correct diagnosis and to appropriately assess the risk in AC.

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