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REVIEW

Exercise and Arrhythmogenic Right Ventricular Cardiomyopathy

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a group of cardiomyopathies associated with ventricular arrhythmias predominantly arising from the right ventricle, sudden cardiac death and right ventricular failure, caused largely due to inherited mutations in proteins of the desmosomal complex. Whilst long recognised as a cause of sudden cardiac death (SCD) during exercise, it has recently been recognised that intense and prolonged exercise can worsen the disease resulting in earlier and more severe phenotypic expression. Changes in cardiac structure and function as a result of exercise training also pose challenges with diagnosis as enlargement of the right ventricle is commonly seen in endurance athletes. Advice regarding restriction of exercise is an important part of patient management, not only of those with established disease, but also in individuals known to carry gene mutations associated with development of ARVC.

Keywords Arrhythmogenic • Cardiomyopathy • Exercise • ARVC • Genetics

Introduction

The term arrhythmogenic cardiomyopathy encompasses a group of cardiomyopathies with a similar phenotype and a tendency to ventricular arrhythmias accompanying or preceding structural and functional changes of the myocardium. The alternate term of arrhythmogenic right ventricular cardiomyopathy (ARVC) reflects the fact that the earliest descriptions of the disease noted patchy inflammation, fibrosis and dysfunction disproportionately affecting the right ventricle (RV), but more recent observations have recognised that the left ventricle is commonly involved, sometimes even in isolation. ARVC (used subsequently reflecting the dominant use throughout contemporary literature) is often caused by abnormalities in desmosomal proteins and is associated with an increased risk of sudden cardiac death (SCD), particularly during exercise. What has also been appreciated more recently is the important interaction of this condition with exercise and athletic training. It has long been known that ARVC is an important cause of sudden cardiac death with exercise [1], but more recently it has been recognised that athletic training can accelerate the progression of the disease [2–4] and also that excessive endurance exercise may be a cause of an ARVC-like phenotype, even in the absence of genetic abnormalities known to be associated with ARVC [5–8]. This review will examine the evidence for the relationship between ARVC, exercise and SCD and the clinical implications of this for patient management.

Pathogenesis of ARVC

Arrhythmogenic cardiomyopathies are due to mutations in genes encoding proteins in the intercalated disc, most commonly desmosomal proteins, which are involved in cell adhesion and cell-to-cell communication. Most cases are due to mutations in one of 5 genes encoding desmosomal proteins; desmoplakin (DSP), plakoglobin (JUP), plakophilin 2 (PKP2), desmoglein 2 (DSG2) and desmocollin 2 (DSC2) (Figure 1). Together these genes account for 40–50% of ARVC cases [9] with PKP2 being the most commonly affected gene. Inheritance is usually autosomal dominant, meaning that

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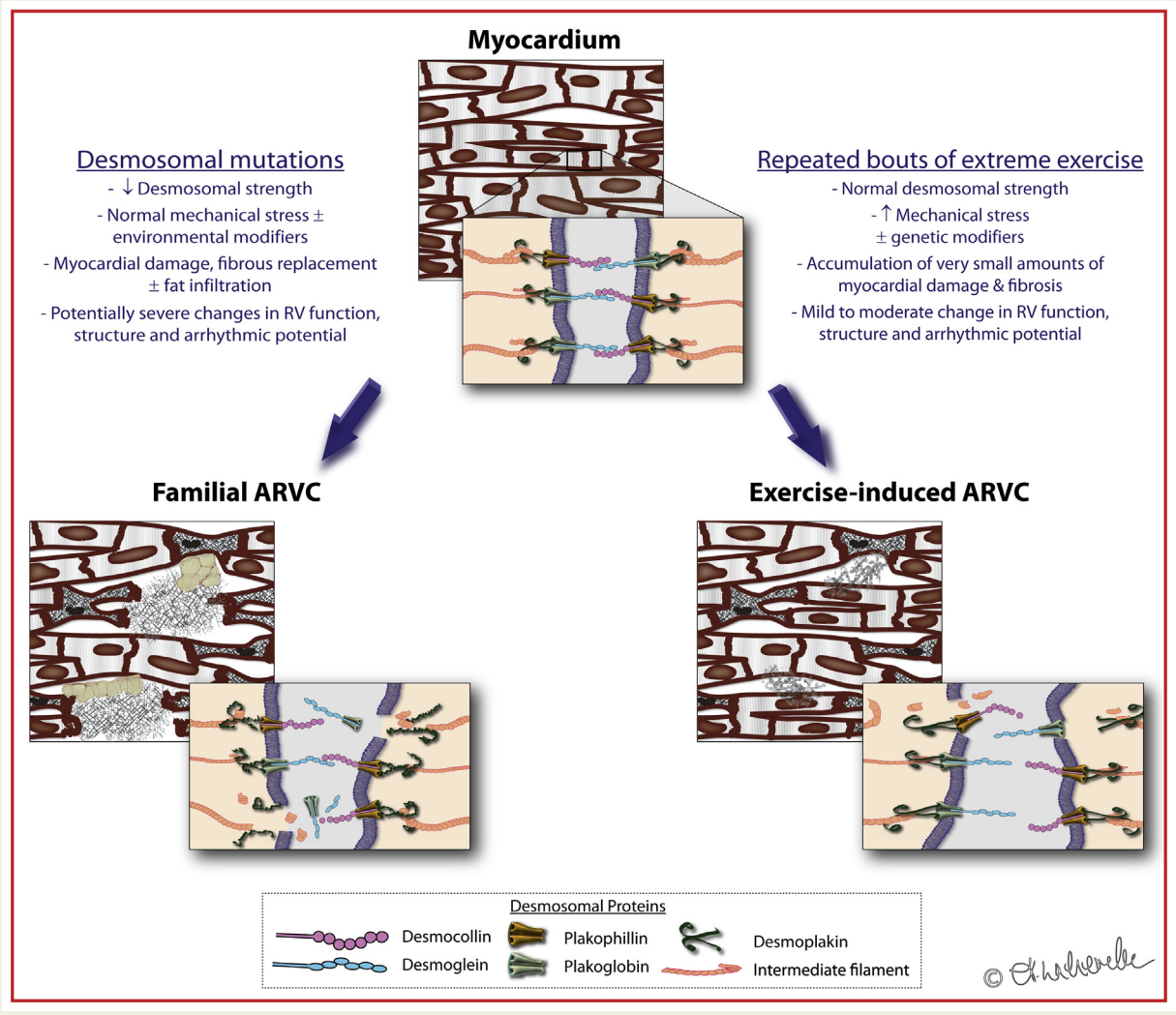

Figure 1 Integrity of the desmosome may be compromised by mutations in the desmosomal proteins. This results in disruption of the myocte junctions leading to development of the arrhythmogenic right ventricular cardiomyopathy (ARVC) phenotype. The addition of repeated bouts of exercise, in the presence or absence of desmosomal mutations, may cause or accelerate disruption of the junctions. Reproduced from Heidbuchel et al. [8].

50% of off-spring of an affected individual will carry the gene mutation and be at risk of developing the ARVC phenotype, although penetrance is incomplete and expression is variable. In some patients (1–16%), mutations are present in more than one ARVC-related gene and the presence of multiple mutations is associated with a more severe phenotype and worse outcomes [10–13].

There have also been mutations in non-desmosomal genes described which also give rise to inherited arrhythmogenic cardiomyopathies. These include cadherin 2 (CDH2), catenin alpha 3 (CTTNA3), transforming growth factor beta 2 (TGFß3), titin, transmembrane protein 43 (TMEM-43), phospholamban (PLN) and lamin (LMNA). There is considerable variability in the resulting phenotype with frequent involvement of the left ventricle. This explains some of the shift in nomenclature to the broader term of arrhythmogenic cardiomyopathy, of which ARVC forms a subset. Future revisions of disease definitions may combine the genetic and clinical aspects of the disease or consider them separately. This is not simple semantics as already there are potential differences in the way in which genetic subsets may respond to environmental stressors such as exercise.

Clinical Presentation of ARVC

Arrhythmogenic cardiomyopathies may come to medical attention in a variety of ways but the earliest manifestation is most frequently with symptomatic ventricular arrhythmias, hence the retention of the word *arrhythmogenic* in all versions of the expanding nomenclature. The spectrum extends,

however, from affected individuals who present with sudden cardiac death to asymptomatic family members of individuals with known disease who carry causative gene mutations. Within the spectrum are those with ventricular arrhythmias, those with right ventricular failure and those with cardiomegaly on a chest X-ray or an enlarged right ventricle on imaging such as echocardiography or cardiac magnetic resonance (CMR). Although the spectrum of disease includes patients in whom structural abnormalities of the RV (or LV) are the dominant finding, initial presentation with heart failure is rare. Rather, heart failure seems to be an end-stage consequence of a long period of symptomatic disease and, intriguingly, is greatly over-represented in those ARVC patients participating in endurance sports [2].

There is a recognised typical pattern of progression of the disease which impacts on the mode of presentation and how it varies with age. The earliest phase may be asymptomatic or concealed disease, but in which the risk of SCD, particularly during exercise, is significant. It is this phase that forms the rationale for screening strategies. The disease may progress to symptomatic and more sustained arrhythmias in the third and fourth decades and later to progressive right heart failure in the fifth decade of life and beyond. However, there is massive variability in phenotypic expression ranging from more fulminant presentations through to genotype positive patients who remain completely free of disease throughout their life. The factors underpinning this variability are complex but it is clear that exercise is a significant modifier of disease expression.

There is some controversy around whether ARVC is a relentlessly progressive disease. Some excellent short- to mid-term outcomes have been demonstrated following electrophysiological procedures in which the abnormal myocardium is modified with ablation [14]. At least some of these patients seem to enjoy a benign clinical course with little or no progression of structural and functional abnormalities. However, the weight of evidence favours a progressive process with a highly variable course, but in which exercise has been repeatedly observed to be a key determinant [15].

Because of the clinical heterogeneity of ARVC, the diagnosis is made using recognised Task Force Criteria (TFC) which incorporate findings in multiple domains including imaging, electrocardiography, electrophysiology, histology and family history [16]. These abnormal findings provide major and minor criteria for a positive diagnosis of ARVC. Diagnosis is considered definite with two major criteria or one major plus two minor criteria. A borderline diagnosis is established with one major plus one minor, or with three minor criteria [16].

The diagnosis of ARVC is made more challenging in endurance athletes because the degree of remodelling of the RV in many healthy athletes meets some of the modified taskforce criteria for ARVC. For example, in a cohort of endurance athletes examined by echocardiography, right ventricular outflow tract (RVOT) size fulfilled a major criterion for ARVC in 25% of athletes, with 50% exceeding the dimension for a minor criterion [17]. Similarly, elite endurance athletes have an increased rate of T-wave inversion in the right precordial electrocardiogram (ECG) leads (V1 to V3) when compared to non-endurance athletes (4% vs 0.2%), a finding which provides one positive task force criterion [18]. This appears to be due to lateral displacement of these dilated hearts such that a greater proportion of the RV is placed situated under the right precordial ECG leads [19]. Thus a dilated RVOT in association with T-wave inversion in a healthy athlete could result in a definite diagnosis of ARVC according to TFC. It is not yet clear whether this ambiguity is clarified or amplified by the more widespread use of cardiac magnetic resonance imaging (CMR). This is discussed in more detail in a specific review article addressing the challenge of differentiating ARVC from the normal athlete's heart [20].

A Mechanism Explaining an Interaction Between Exercise and ARVC

As a result of the alteration of proteins within the intercalated discs, there is disruption of normal cell adhesion and mechanical stability, cell to cell communication and electrical coupling. It has been postulated that this results in instability in the setting of mechanical stress, such as that which occurs with exercise. It has been shown that wall stress on the RV increases more than that on the LV during exercise [21], an observation which may explain part of the predilection for desmosomal mutations to impact the RV more than the LV. Using a simple analogy, if the desmosomes represent the 'glue' connecting the myocytes then disease can become manifest by weakness of the glue (genetic mutations of the desmosomes), by high mechanical force on the glue (intense exercise) or both (see Figure 1). This concept of an interaction between genetic and environmental stressors combining to variable extents to result in overt disease is summarised in Figure 2. Since the earliest descriptions of ARVC, it was recognised that there was loss of myocytes within the right ventricle and replacement by fibrous and fatty tissue [22]. This may be due to myocyte apoptosis resulting from abnormalities in cell signalling due to the disruption of the desmosomes and connexins [23] resulting from the combination of host genetic and environmental factors.

Some histologic and imaging studies have identified areas of inflammation within the myocardium in ARVC supporting a possible role for an inflammatory process in the development and progression of the disease [24,25]. There has been debate about whether some sporadic cases may have more predominant virally triggered inflammatory pathogenesis or whether the inflammation is simply a marker of a more active phase of the disease [26] or even a reaction to cell death. Whether inflammatory cytokine release during exercise acts as a trigger for myocardial inflammation or whether mechanical stress alone is the trigger for disease progression in ARVC is unknown. There

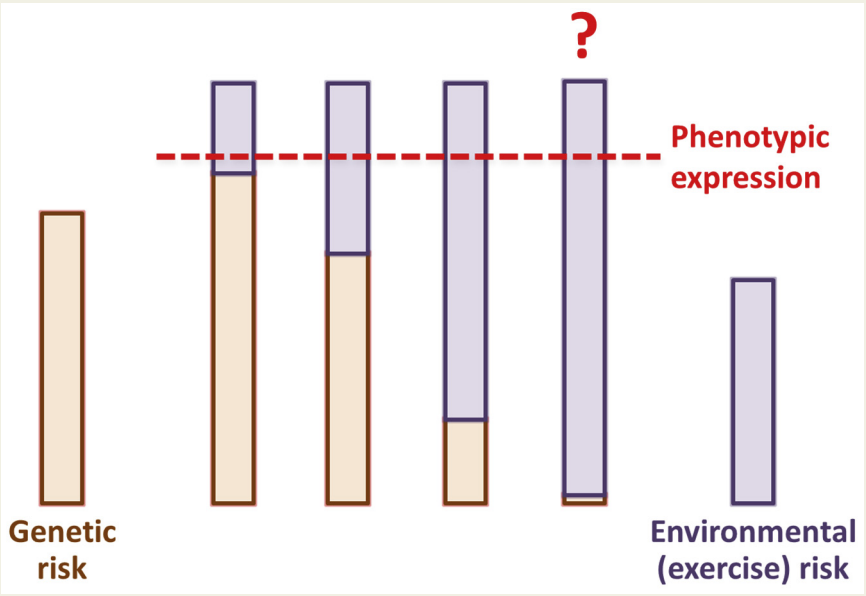

Figure 2 The balance between genetic and environmental factors such as exercise in the phenotypic expression of arrhythmogenic right ventricular cardiomyopathy (ARVC). Individuals with high genetic risk may express the disease with little or no exercise contribution. Individuals with lower genetic risk may require more intense of prolonged exercise to express ARVC. Reproduced from La Gerche [55].

is some support for a connection between pro-inflammatory cytokines and acute RV damage following prolonged intense exercise [27].

The concept of an exercise and genetic interaction has also been appraised in pre-clinical models. Animal studies in plakoglobin deficient mice have provided supporting information about the impact of exercise on development and progression of disease in ARVC [28]. Kirchhof et al. studied heterozygous plakoglobin-deficient mice, some of which undertook daily swim training. Whilst the sedentary plakoglobin-deficient mice developed gradual enlargement of the right ventricle over 10 months, when compared to wild-type mice, the trained mice developed more severe RV enlargement after only 6 months and this was associated with a high rate of spontaneous ventricular tachycardia of right ventricular origin. This parallels clinical observations in humans.

In another mouse model of ARVC, phenotypic expression of a PKP2 mutation was only seen in animals who were subjected to an 8-week endurance swim training protocol and not in sedentary mice [29]. Sedentary mice did not develop abnormalities on CMR independent of whether they expressed the PKP2 mutation. In contrast, control mice who exercised maintained a normal right ventricular ejection fraction (RVEF), whereas RVEF was reduced in the endurance trained carriers of the mutation. These animal studies support the concept that in the presence of an ARVC causing mutation, exercise is a trigger associated with phenotypic expression and more rapid progression of the ARVC phenotype.

Similar to some human studies, pre-clinical models also support the concept that more extreme exercise may cause ARVC-like changes even in the absence of a genetic predisposition. In a study using male Wistar rats without known arrhythmogenic gene mutations, vigorous running exercise alone produced fibrosis in the right ventricle and atria resulting in a predisposition to RV arrhythmias with programmed electrical stimulation [30]. These changes were not observed in rats that did not undergo vigorous exercise training.

ARVC as a Cause of Sudden Cardiac Death During Exercise

Whereas the original case series describing ARVC identified it as a cause of ventricular arrhythmias and right heart failure [22], a subsequent post-mortem study identified ARVC as an important cause of sudden cardiac death in young people with no clinical history of arrhythmias [31]. The same group from the Veneto region of Italy later identified ARVC as an important cause of sudden cardiac death during exercise [1], associated with a five-fold increase in risk when compared to sedentary individuals with the same disease. Reports from other parts of the world support ARVC as an important cause of SCD during exercise [32], although the frequency of this entity was lower in non-Italian locations with other inherited and acquired diseases such as hypertrophic cardiomyopathy, coronary anomalies and myocarditis being more prominent [33–35]. In a Canadian series of 74 cases of SCD, there were no cases due to ARVC [36].

In some countries, screening of young athletes for conditions associated with SCD during exercise has been recommended and adopted [37,38]. Whilst there have been no randomised trials of this approach, longitudinal data from Italy show a fall in the rate of SCD during exercise after the introduction of systematic screening [39]. Perhaps surprisingly, although ARVC was a dominant cause of SCD prescreening, only a minority of athletes were excluded from participation due to a diagnosis of ARVC as a result of screening.

Effect of Competitive Exercise on Progression of ARVC

Whilst the role of exercise as a trigger for SCD has been long understood, more recent data suggest that exercise is an important modulator of the phenotypic expression, progression and prognosis of ARVC. It was observed that in carriers of mutations in ARVC genes, symptoms occurred at a younger age (around 10 years earlier) in those undertaking endurance exercise when compared to sedentary individuals and they were more likely to have ventricular arrhythmias and heart failure than those who did the least amount of exercise [2,4]. Endurance exercise was also associated with a higher rate of developing positive task force criteria for ARVC. Imaging studies in both patients with ARVC and mutation-positive family members revealed that left and right ventricular function was reduced in athletes when compared to non-athletes [3]. One (1) smaller study examined the intensity of dynamic physical activity in the 10 years preceding a diagnosis of definite ARVC and subsequently followed these individuals for a mean of 6.8 years [40]. They found that those with the highest intensity of exercise were more likely to have an arrhythmic event or to develop RVEF $<35\%$ than those with a history of moderate exercise, who were in turn more likely than those who were inactive. Similarly, in a cohort of patients with arrhythmogenic cardiomyopathy and mutation positive family members, a history of high intensity exercise was a strong predictor of life-threatening arrhythmias with an eight-fold increase in risk over a median of 4.2 years follow-up [41]. Thus, presymptomatic genetic diagnosis may provide important information on which to base advice regarding exercise for gene mutation carriers. It is reasonable to argue that those individuals with disease-causing mutations should be counselled against endurance and competitive exercise to prevent disease development and this is reflected in recent European guidelines [42].

When a cohort of endurance athletes with right ventricular arrhythmias were examined for the presence of mutations in the five most common genes known to cause ARVC, those with recognised mutations had worse RV function, but had engaged in less exercise than those without mutations, thereby supporting a role for exercise in progression of ARVC in gene positive athletes [6]. Furthermore, several endurance athletes met criteria for ARVC but only a small minority (12%) had a desmosomal gene mutation, suggesting that an ARVC-like phenotype can occur in athletes in the absence of a disease-causing mutation. Thus, endurance exercise appears to accelerate the progression and expression of ARVC in those with desmosomal mutations in a dose-dependent fashion and potentially may cause ARVC in those without a clear genetic predisposition if the exercise exposure is sufficiently large (Figure 2). This has implications for management of genotype positive/phenotype negative carriers and those with phenotype positive disease.

Exercise-Induced ARVC

Some endurance athletes have been reported to develop a syndrome of ventricular arrhythmias arising from the right side of the heart [5], sometimes accompanied by abnormalities of right ventricular structure and function, present either at rest [43] or elucidated with exercise testing [44]. It has been suggested that this entity is simply a cohort of unrecognised cases of ARVC. However, as noted above, genetic testing in one group of athletes with right ventricular arrhythmias revealed a lower-than expected prevalence of recognised gene mutations than would be seen if all cases in this cohort were simply due to due to unrecognised ARVC, rather than a distinct exercise-induced variant [6]. Approaching the same question from a different direction, in a study of patients with a clinical diagnosis of ARVC, patients in whom a desmosomal mutation was not identified (termed 'gene-elusive' by the investigators) had a strong association with very high intensity exercise [45]. In fact, 100% of patients without a recognised desmosomal mutation ('gene-elusive' ARVC patients) were endurance athletes vs only 70% of the gene-positive group. They had a lower rate of a positive family history and were more likely to present at age ≤ 25 years, particularly those with the greatest amount of premorbid exercise.

These findings support the presence of an exercise-induced ARVC phenotype, particularly with endurance exercise. As mentioned previously, this concept is also supported by the findings of Benito et al. [30] in which an ARVC phenotype could be elicited by vigorous exercise in rats without a known genetic predisposition. On the other hand, it is clear that only a minority of highly-trained athletes are affected despite similar exercise training exposure. It is also possible that these individuals carry a mutation in a gene which is not expressed phenotypically unless subjected to the environmental trigger of endurance exercise. The animal work of Cruz et al. would support this hypothesis [29]. This raises the possibility that there are other modifying factors, both genetic and environmental. The current model of inherited ARVC is that of a monogenic disorder, but it is also possible that a combination of genetic modifiers creates the condition in which exercise may promote myocyte injury and resulting arrhythmias. Other environmental influences such as concurrent illness, particularly whilst training, is another plausible modifier.

Exercise Prescription in ARVC

Because high level exercise is known to accelerate the progression of ARVC and increase the risk of sudden death, individuals with the diagnosis need clear advice about how much exercise is safe. It would seem prudent to provide advice both to those with a definite diagnosis of ARVC and to those who carry a mutation known to cause ARVC. Unfortunately, there is little systematic evidence to guide this and most advice is based upon expert opinion. Advice to only exercise moderately will have a different meaning to a former professional athlete when compared to a sedentary individual.

The greatest advances in our evidence base for exercise advice have come from studies of ARVC registries at Johns Hopkins in Baltimore and from Oslo in Norway. James et al. observed that exercise restriction after the diagnosis of ARVC had a direct impact on clinical outcomes [2]. In dividing exercise exposure into quartiles, they observed that the highest rates of life-threatening arrhythmias occurred in those patients who performed the most exercise before and after diagnosis [2]. However, in those who reduced their exercise from the highest quartile to the lower quartiles the risk of ventricular tachycardia/ventricular fibrillation (VT/VF) fell from 75% to 12%. To some extent the reverse was also true. In those who exercised less, the arrhythmias tended to be more common if patients increased exercise to the highest quartile after diagnosis (from 10% to 29%) although this difference was not significant [2].

More recently, Sawant and colleagues from Johns Hopkins enabled clinicians to be a little more specific with advice regarding exercise dose by studying 10 extended families with plakophilin mutations [46]. Endurance athletes were disproportionately represented amongst those family members meeting Task Force Criteria for a diagnosis of phenotype positive ARVC (67% vs. 23%, p=0.03). Similarly, of six family members to experience at least one bout of VT/VF, all six (100%) were endurance athletes whereas endurance athletes only comprised 41% of those without VT/VF (p=0.02). Importantly, in seven family members who performed exercise at or below American Heart Association guidelines of 150 minutes/week of low to moderate intensity, only one met Task Force Criteria and none developed ventricular arrhythmias. This study was of modest size, but does provide some confidence on which to recommend that people can afford to continue to exercise to a modest degree whilst undergoing regular follow-up to monitor disease progression.

The Norwegian group of Lie et al. assessed the relative effects of exercise and intensity and their relationship to disease progression in patients with ARVC and genopositive family members [47]. They observed more prevalent ventricular arrhythmias in patients performing exercise of greater intensity (74% vs. 20% performed >6 METS, $p<0.001$) and volume (65%, vs 30% exercised >2.5 hours/week, $p<0.001$). However, on multivariate analysis, intensity rather than duration was independently associated with arrhythmias. This provides further support for recommendations to our patients that exercise should be limited to less than 2.5 hours per week but even more importantly that intense exercise should be avoided.

A further question relates to exercise in patients with implantable cardiac defibrillators (ICDs). Whilst a more liberal approach to participation is supported by observations of few serious arrhythmias and no deaths in competitive and recreational athletes with devices [48,49], there has been concern that a more permissive approach should not be extended to athletes with ARVC because of the risk of progression. In support of this, Wang et al. found that those with ARVC who reduced exercise dose (a combination of intensity and duration) experienced the greatest reduction in arrhythmia events [50]. Intriguingly, the group that experienced the greatest benefit from detraining was the 'gene elusive' patients and those in whom the device was implanted for primary prevention. One might extrapolate to conclude that those with exercise-induced ARVC (the majority of gene negative ARVC patients) at a relatively early stage (before arrhythmias) are the group who particular focus on detraining should be directed.

Currently, there is no research relating to weight or strength training in patients with ARVC and in the absence of evidence we tend to be conservative. However, there is at least some physiological rationale to speculate that weight training may be well tolerated by patients with ARVC. As discussed earlier in this review, the mechanistic postulate underpinning the association between exercise and ARVC relates to the excess in ventricular wall stress that occurs during exercise. This is particularly influenced by the volume load and 'stretch' of exercise that results in both acute load and long-term remodelling in the form of cardiac dilation. Strength training causes little volume load and little long-term remodelling. The Morganroth hypothesis argued that endurance exercise caused a volume load and ventricular dilation whereas strength training caused a pressure load and resulting hypertrophy [51]. However, multiple intervention studies have failed to demonstrate significant remodelling with strength training [52]. Thus, there is reason to argue that strength training causes little or no acute

Table 1 Pragmatic exercise advice in ARVC and in gene positive carriers.

1. Endurance exercise should be avoided.
2. Exercise should be limited to less than 2.5 hours per week
3. Intense exercise should be avoided. Patients should be encouraged to exercise well below ventilatory threshold. Simple guidance like exercising at a level where you can maintain conversation may be useful.
4. Moderate static strength-based exercise may be reasonable.

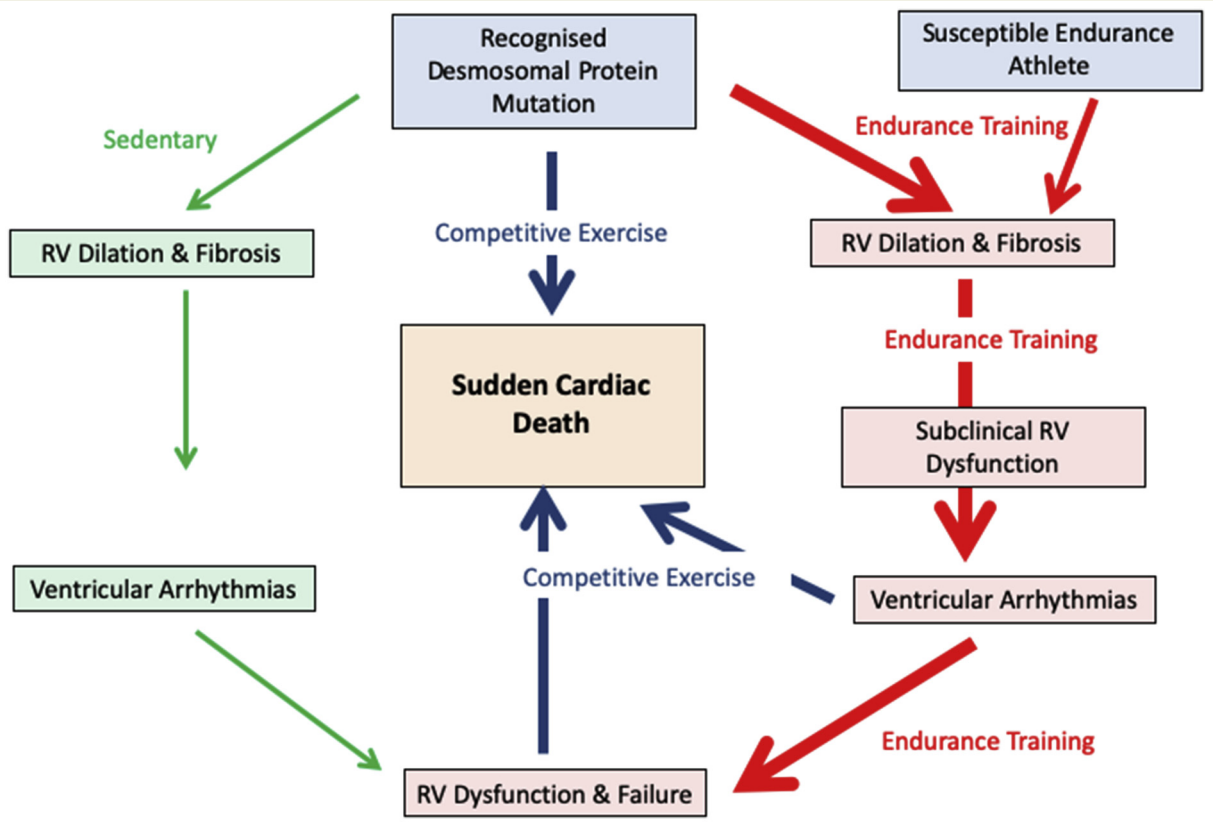

Figure 3 The complex relationship between exercise, ARVC, sudden death and ventricular arrhythmias. Competitive and endurance exercise accelerates the expression and progression of ARVC leading to ventricular arrhythmias and RV dysfunction at a younger age.
Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; RV, right ventricular.

haemodynamic stress, such that it would not be expected to exacerbate ARVC. In trying to summate the evidence from the observational studies discussed above and our own theories on the role of exercise in ARVC pathogenesis we have created pragmatic recommendations for exercise (Table 1).

The most recent expert consensus from the Heart Rhythm Society recommends counselling individuals who are genotype positive-phenotype negative that competitive or frequent high-intensity endurance exercise is associated with increased likelihood of developing ARVC and ventricular arrhythmias. The advice for individuals with a diagnosis of ARVC is that they should not participate in competitive or frequent high-intensity endurance exercise [53]. An international task force on treatment of ARVC made an additional class IIa recommendation that patients with a definite diagnosis of ARVC should be restricted from participation in athletic activities, with the possible exception of recreational low-intensity sports [54]. The most recent European guidelines regarding management of athletes with cardiomyopathies state that patients with ARVC should not compete in competitive sports and extend the same recommendation to those with a desmosomal mutation, but without overt disease [42].

Apart from exercise restriction, management of patients with ARVC will include stratification of risk for SCD based on clinical, electrophysiological and imaging parameters. Genetic counselling and screening of relatives remain important components of management. Treatment of arrhythmias may include antiarrhythmic drug therapy, electrophysiology study, VT ablation and implantation of a defibrillator [54]. In those with right heart failure, medications including diuretics, mineralocorticoid receptors antagonists, angiotensin converting enzyme inhibitors, beta blockers and nitrates are all considered reasonable [53]. In those with severe arrhythmias or right heart failure, heart transplantation may be an option. The choice of treatment options should be individualised.

Conclusion

Arrhythmogenic right ventricular cardiomyopathy interacts with exercise in multiple ways which are all of clinical importance (Figure 3). It is an important cause of SCD during exercise in the young. Phenotypic expression and severity of ARVC are worsened by exercise, particularly endurance

exercise. Extreme endurance exercise has been implicated in the development of and exercise-induced ARVC syndrome, even in the absence of gene mutations recognised to cause ARVC. For these reasons, advice regarding exercise restriction forms a major component of the management of this condition.

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