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Arrhythmogenic Right Ventricular Cardiomyopathy: Progress Toward Personalized Management

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arrhythmogenic right ventricular cardiomyopathy, exercise, implantable cardioverter defibrillator, genetic testing, ventricular tachycardia, desmosome

Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart disease characterized by fibrofatty replacement of the ventricular myocardium, a high risk of ventricular arrhythmias, and progressive ventricular dysfunction. The clinical course is highly variable, and optimal approaches to management remain undefined. ARVC is associated with pathogenic variants in genes encoding the cardiac desmosome. Genetic testing facilitates identification of at-risk family members, but penetrance of ARVC in pathogenic variant carriers is difficult to predict. Participation in endurance exercise is a known key risk factor. However, there remains significant uncertainty about which family member will develop disease and how best to approach longitudinal screening. Our clinically focused review describes how new insights gained from natural history studies, improved understanding of pathogenic mechanisms, and appreciation of genetic and environmental modifiers have set the stage for developing personalized approaches to managing both ARVC patients and their at-risk family members.

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by frequent ventricular arrhythmias, a high risk of sudden cardiac death, and progressive ventricular dysfunction (1). While relatively rare (prevalence 1/2,500–1/5,000), ARVC is an important cause of sudden cardiac death in young individuals and athletes (2). ARVC is typically an inherited, autosomal dominant condition with reduced penetrance and markedly variable expressivity (3).

ARVC was first described in the literature in 1982 (4). The past decade has been characterized by rapid progress in understanding its genetic architecture and molecular pathophysiology. Simultaneously, large, international observational studies have significantly advanced our understanding of the natural history of both affected patients and at-risk family members (5, 6). A growing number of genomic, environmental, and clinical factors have been implicated in ARVC pathogenesis and associated with disease penetrance and progression. These discoveries set the stage for addressing a central challenge of managing ARVC patients and families: the striking clinical heterogeneity among both patients and at-risk family members.

This review summarizes these advances, describes how they inform best practices for care of ARVC patients and families, and discusses the resulting new initiatives toward evidence-based, personalized management.

CLINICAL SUMMARY AND NATURAL HISTORY

The pathophysiological hallmark of ARVC is progressive fibrofatty replacement of the ventricular myocardium, which provides a substrate for ventricular arrhythmias (7). In addition, gap junction and ion channel remodeling, which occurs early in the disease process, promotes catecholamine-facilitated ventricular arrhythmias (8, 9). It is not surprising, therefore, that ARVC index cases typically come to medical attention with symptoms associated with ventricular arrhythmias, including palpitations, syncope, sudden cardiac arrest, or sudden cardiac death. In the largest ARVC cohort to date (5), 95% of 439 ARVC probands were symptomatic at diagnosis; more than half (56%) presented with sustained ventricular tachycardia and an additional 11% with sudden cardiac death or resuscitated arrest. Family members benefit from cascade screening and are frequently asymptomatic at diagnosis.

Diagnostic Criteria

ARVC diagnosis is based on the 2010 Task Force Criteria (10), which integrate results of cardiac and genetic testing with family and clinical history. Major and minor criteria are assigned in six categories: repolarization abnormalities, depolarization abnormalities, right ventricular enlargement and dysfunction, fibrofatty replacement on cardiac biopsy, ventricular arrhythmias, and genotype and family history of ARVC. A definite ARVC diagnosis is established when a patient meets at least two major, one major and two minor, or four minor criteria from different categories. The current criteria were developed with the intent of improving diagnostic sensitivity by including quantitative measures of cardiac structure and function, adding new repolarization and depolarization criteria derived from the electrocardiogram, and integrating genotype. While this approach has led to robust identification of patients with right-predominant disease and also facilitated early diagnosis of family members (11), there is recognition that the 2010 criteria are not sufficiently sensitive for patients with biventricular or left-predominant presentations (12), and many experts in the field argue the criteria should be updated. Studies to prospectively validate the 2010 criteria and identify strengths and weaknesses are a vital next step to guide development of a new diagnostic algorithm.

Natural History

Recent data from large cohorts diagnosed according to the 2010 criteria have provided new insight into the natural history of ARVC and identified clinical and demographic characteristics associated with its clinical course (11, 13). Given (a) the wide clinical variability among ARVC patients, (b) the relative rarity and underrecognition of ARVC, and (c) the high prevalence of sudden death as a first symptom, international collaboration has been critical to advancing understanding of the natural history of ARVC.

The largest ARVC cohort diagnosed according to the 2010 criteria included 1,001 ARVC index cases and at-risk family members identified from the Johns Hopkins and Dutch ARVC Registries (5). Other key data have been derived from cohorts from the Swiss and Nordic Registries, national centers with decades of ARVC expertise, and the North American ARVC Registry supported by the National Institutes of Health (NIH). Taken together, studies from these cohorts have established that ARVC patients typically present between adolescence and mid-adulthood (average age 35.1 ± 14.9). Reports of prepubertal children with ARVC have been rare (14). Among 75 patients with pediatric-onset ARVC in a combined US-Dutch cohort, there was no patient diagnosed prior to 11 years of age (15). Studies have established that the risk of ventricular arrhythmias rises rapidly in adolescence (16), and adolescents are most likely to present with sudden cardiac death (15). At the other end of the age spectrum, one-fifth of ARVC patients in the Johns Hopkins/Dutch cohort presented at age 50 or older, and 3% were diagnosed after age 65 (17). These patients were more likely to present with sustained ventricular tachycardia, but their clinical courses were otherwise indistinguishable from those of younger patients.

Complex ventricular arrhythmia, including presentation with sudden cardiac death, is frequently associated with ARVC. A recent meta-analysis including 28 studies of definite ARVC patients showed an average rate of sustained ventricular arrhythmias of 10.6% per year (range 3.0–30.1%) (18). Placement of implantable cardioverter defibrillators (ICDs) to prevent sudden cardiac death is thus a common management decision. Series of ARVC patients with ICDs report high rates of appropriate ICD therapy (19, 20). In a recent cohort of 312 definite ARVC patients with ICDs (21), as shown in **Figure 1a**, cumulative survival free from appropriate ICD interventions was 60%, 51%, 37% and 24% at 1, 2, 5 and 10 years, respectively. **Figure 1b** highlights ARVC patients' relatively high risk of requiring ICD therapy for a rapid ventricular arrhythmia (cycle length ≤ 240 msec).

Should sudden cardiac death be prevented, most ARVC patients have a favorable prognosis. Mortality rates ranged from 1% to 2% per year in recently published cohorts (5, 16, 22, 23). Most deaths were associated with sudden cardiac arrest in patients without ICDs or with heart failure and transplant.

While ICDs have been shown to reduce mortality in ARVC (19), living with frequent ventricular arrhythmias is associated with psychological morbidity. ARVC patients experience high levels of generalized, cardiac, and ICD-related anxiety (24). Clinically significant anxiety is highest in younger patients with recent diagnoses and history of ICD shocks. Furthermore, ARVC patients have reduced physical and mental quality of life (25).

Heart Failure and Structural Progression

ARVC is often characterized by progressive cardiac dysfunction. Several studies have documented worsening right and left ventricular function and progressive ventricular enlargement (26, 27). The rate of structural progression is heterogeneous, and predictors remain largely elusive (28). Furthermore, recent research suggests that the frequency of heart failure in ARVC has been underappreciated (29). In most ARVC cohorts, heart failure is reported in only 4–16% of patients

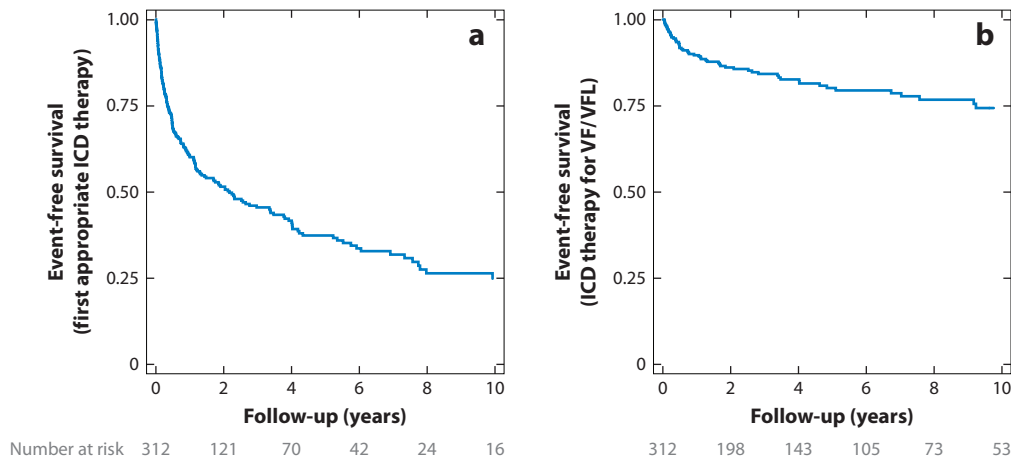


Figure 1

Survival free from appropriate implantable cardioverter defibrillator (ICD) therapy in 312 definite arrhythmogenic right ventricular cardiomyopathy patients. (a) Kaplan-Meier analysis of cumulative survival free from any appropriate ICD intervention. (b) Kaplan-Meier analysis of cumulative survival free from ventricular fibrillation/ventricular flutter (VF/VFL). Adapted from Reference 21 with permission.

(13, 30). However, a recent study focused on defining prevalence of signs and symptoms of both left- and right-sided heart failure showed that 49% of ARVC patients met criteria for clinical heart failure (29). Classic left-sided symptoms were relatively rare, as was the presence of heart failure at diagnosis. Patients with heart failure were more likely to require cardiac transplant and to die in follow-up. With improvements in treating arrhythmias and preventing sudden cardiac death, it may be that patients with more severe phenotypes are surviving severe arrhythmias early in the course of the disease, and thus we are uncovering a new natural history of advanced structural disease in these survivors. There is much to learn about how best to predict, detect, and manage the predominantly right-sided heart failure in ARVC. We anticipate that this will be a growing area of ARVC research in the next decade.

Toward Individualized Arrhythmia Risk Prediction

While heart failure and structural progression in ARVC remain to be precisely defined, the now well-described arrhythmic course of ARVC leaves the research community prepared to develop approaches for individualized prediction of risk of life-threatening ventricular arrhythmias to inform decision making for ICD placement. There is agreement that most ARVC patients with a prior history of sustained ventricular arrhythmias or resuscitated sudden cardiac arrest benefit from ICD placement (31). However, for patients who have not yet experienced a sustained ventricular arrhythmia, there is no established risk stratification scheme. Previous studies in primary prevention ARVC populations show annual event rates of 2–10%. The largest study of primary prevention ARVC patients ($n = 106$ with ICDs) identified syncope as a significant predictor for appropriate ICD therapy (20). In a smaller group of primary prevention ARVC patients, only non-sustained ventricular tachycardia and inducibility on electrophysiology study were independent predictors of appropriate ICD therapy (32). Many clinicians would conclude that an ICD implant is reasonable for most ARVC patients, given the high event rate and limited available predictors. However, ICD placement has important drawbacks in this usually young and active population,

with a substantial rate of complications and inappropriate shocks (21, 33). Appropriate patient selection is therefore critical.

A recent meta-analysis that examined the association of clinical and demographic variables with ventricular arrhythmias in ARVC patients identified male sex, cardiac syncope, t-wave inversions beyond V3, right ventricular dysfunction, and a prior history of ventricular arrhythmias as predictors of sustained ventricular arrhythmias in follow-up (18). This work also highlighted the shortcomings of these studies, most critically the relatively small patient populations and thus insufficient statistical power to assess the independent predictive value of potentially correlated risk factors. The consensus-based algorithm for ICD placement published in the International Task Force Consensus Statement for treatment of ARVD/C in 2015 (31) was an important attempt to integrate this literature to inform decision making about ICD placement. The risk strata of this algorithm distinguish degrees of arrhythmia risk reasonably well but have limitations when applied to primary prevention patients, and recent data suggest that integrating the results of Holter monitoring would improve the algorithm (34).

Leaders of international ARVC registries from 6 countries (14 centers) have now come together to develop a model based on readily available, noninvasive clinical parameters to generate individualized risks of developing ventricular arrhythmias for ARVC patients who have not experienced a sustained ventricular arrhythmia prior to diagnosis. Data analysis is well under way (35). The potential utility of this approach is illustrated by integration of a similarly derived model into international treatment guidelines for hypertrophic cardiomyopathy (36). We anticipate that the model will help set the standard for shared decision making for ICD placement in ARVC.

MOLECULAR PATHOPHYSIOLOGY AND NEW PATHOPHYSIOLOGIC FINDINGS LEADING TO A CLINICAL TRIAL FOR ARRHYTHMIA MANAGEMENT

Other opportunities for personalized approaches to ARVC management have leveraged discoveries of the molecular mechanisms of ARVC pathogenesis. ARVC is broadly considered a disease of the desmosome (3). Following the key discovery that Naxos disease, a rare cardiocutaneous autosomal recessive form of ARVC, was caused by pathogenic variants in the gene encoding plakoglobin (*JUP*) (37), there was rapid discovery of pathogenic variants in each of the genes encoding components of the cardiac desmosome in ARVC patients (38–41). Cardiac desmosomes are adhesion junctions composed of a symmetrical group of proteins (cadherins, armadillo proteins, and plakins) that provide mechanical connections between cardiomyocytes. In most ARVC populations, heterozygous variants in *PKP2* resulting in premature termination of the protein product or abnormal splicing are most prevalent (6). The current understanding of the molecular pathways through which desmosomal mutations lead to ARVC pathogenesis has recently been reviewed (3) and is not described in detail here. Instead, we highlight how the new understanding of the molecular pathophysiology of *PKP2* mutations, combined with results of observational studies, led to a planned pilot clinical trial.

To date, antiarrhythmia drug therapy has not been shown to effectively reduce arrhythmias in ARVC. Analysis of the effects of antiarrhythmia medications in 95 patients from the North American ARVC Registry showed that sotalol was associated with a higher risk of sustained ventricular arrhythmia or appropriate ICD therapy and beta blockers with no difference in arrhythmia risk (42). Amiodarone seemed to be more effective, but only 10 patients in the registry were receiving this medication. A recent analysis of a large Italian cohort similarly showed that no anti-arrhythmia medication reduced the rate of ventricular arrhythmias, having compared

matched periods before and after initiation of the drug (16). Thus, there is ample opportunity to improve medical management of ventricular arrhythmias in ARVC.

Recent work has suggested that plakophilin-2 plays a key role in the maintenance of genes involved in intracellular calcium cycling in addition to being critical to cell–cell adhesion of myocytes (43). Specifically, *PKP2* mutations may result in impaired regulation of intracellular calcium cycling with increased ryanodine receptor–dependent calcium release. The investigators further showed that increases in triggered activity and sarcoplasmic reticulum calcium release could contribute to adrenergic-induced arrhythmias in a murine model with cardiac-specific tamoxifen-induced *PKP2* deficiency. Ventricular arrhythmias in the mice were prevented by flecainide infusion. These data are important because ARVC patients have a high prevalence of catecholamine-facilitated ventricular arrhythmias (44), and induction of ventricular tachycardia by isoproterenol infusion is highly sensitive for ARVC diagnosis and predictive of arrhythmias in follow-up (45, 46). Preliminary data from patients are also promising. Among eight ARVC patients with recurrent ventricular arrhythmias who had failed several medications, six had a near-elimination of ventricular arrhythmias when placed on flecainide (47).

These data have set the stage for a pilot randomized double-blinded placebo-controlled crossover trial of the safety and efficacy of flecainide in ARVC patients with >500 premature ventricular contractions per day and preserved left ventricular ejection fraction. Whether efficacy will be genotype specific is an intriguing question.

GENETIC ARCHITECTURE OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Today, pathogenic variants (e.g., mutations) in the desmosomal genes can be detected in approximately half of ARVC probands (5). **Table 1** lists ARVC-associated genes, prevalences of pathogenic variants in contemporary ARVC cohorts, and associated phenotypes. The area composita, a special cardiac-specific mixed-type adhering junction connecting single cardiomyocytes, is emerging as a potentially important cause of ARVC. Pathogenic or likely pathogenic variants in *CTNNA3* [which encodes α T-catenin (48)] and in *CDH2* [which encodes cadherin-2 (49)] were identified in several ARVC families. Variants in genes associated with other cardiomyopathies and arrhythmia syndromes have been reported in ARVC patients, including in the sarcomere genes (50), *DES* (desmin) (51), *TTN* (titin) (52), *LMNA* (lamin A/C) (53), *PLN* (phospholamban) (54), *SCN5A* ($\text{Na}_v1.5$) (55), and *FLNC* (filamin C) (56). These findings highlight the genetic heterogeneity of cardiomyopathies and arrhythmia syndromes. Furthermore, patients have been identified with multiple pathogenic variants (typically compound heterozygous or digenic) (6, 57, 58). However, some of the highest levels reported (up to 21%) are likely an artifact of poor early adjudication of the pathogenicity of missense variants resulting from underappreciation of the frequency of rare variants in the general population. Convincing evidence is emerging that, particularly for *DSG2* and *DSC2*, many carriers have a second variant (59, 60). Finally, a significant number of ARVC index cases have no detectable pathogenic variant. In the largest cohort reported thus far, of 439 index cases, 37% had no mutation in the desmosomal genes, *PLN*, or *TMEM43* (5). These patients are disproportionately athletes (61).

Toward Optimizing Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy

This growing appreciation of the genetic architecture of ARVC has implications for optimizing genetic testing—a Class I recommendation of the Heart Failure Society of America (62). In a

Table 1 ARVC-associated genes, prevalence of pathogenic variants in contemporary ARVC cohorts, and associated phenotypes

| Gene | Protein | Prevalence | Phenotype and notes on inheritance |
|--------------------------------|--------------------------|---|--|
| Desmosomal | | | |
| <i>PKP2</i> | plakophilin-2 | 20–46% | Classic ARVC |
| <i>DSP</i> | desmoplakin | 3–15% | Heterozygous variants: ARVC, frequent biventricular involvement; also causes dilated cardiomyopathy Rare homozygous variants: Carvajal syndrome (cardiocutaneous) |
| <i>DSG2</i> | desmoglein-2 | 3–20% | ARVC, frequently biventricular; also causes dilated cardiomyopathy |
| <i>DSC2</i> | desmocollin-2 | 1–15% | ARVC |
| <i>JUP</i> | plakoglobin | 0–1% (Naxos, Greece) | Naxos disease (cardiocutaneous) |
| Area composite | | | |
| <i>CTNNA3</i> | α T catenin | 0–2%? | ARVC; few cases reported |
| <i>CDH2</i> | cadherin-2 | 0–2%? | ARVC; few cases reported |
| Founder mutations | | | |
| <i>PLN</i> | phospholamban | 0–4% (30% in Dutch population) | ARVC, frequently biventricular, older age of onset. Also causes dilated cardiomyopathy. Dutch founder mutation |
| <i>TMEM43</i> | transmembrane protein 43 | 0–2% (frequent in Newfoundland, Canada) | ARVC, highly lethal ventricular arrhythmias in male carriers. Canadian (Newfoundland) founder mutation |
| Other/overlap syndromes | | | |
| <i>SCN5A</i> | Nav1.5 | 2% | ARVC. Also causes Brugada syndrome, dilated cardiomyopathy, long QT syndrome |
| <i>LMNA</i> | lamin A/C | 0–4% | Overlap with dilated cardiomyopathy |
| <i>DES</i> | desmin | 0–2%? | ARVC association questionable; 1 of two cases detected with <i>PKP2</i> mutation |
| <i>FLNC</i> | filamin C | 0–3% | Arrhythmogenic cardiomyopathy with left-sided predominance; ARVC has been reported |
| <i>TTN</i> | titin | 0–10% | Overlap with dilated cardiomyopathy |

Abbreviation: ARVC, arrhythmogenic right ventricular cardiomyopathy.

recent analysis of a cohort of ARVC patients from our program who underwent testing for a broad panel of cardiomyopathy genes, 9% had pathogenic or likely pathogenic variants detected in a nondesmosomal gene, suggesting the utility of a broad cardiovascular panel for these patients (63). Not surprisingly, variants of uncertain significance were detected at an increased rate. In addition, it is difficult to determine the pathogenicity of a variant in a gene that was unanticipated

based on the patient's phenotype. Indeed, the association of several nondesmosomal putative ARVC genes with the disease has yet to be confirmed. This process is under way among the gene curation activities of the Dilated Cardiomyopathy/ARVC Expert Panel under the auspices of ClinGen. ClinGen is an NIH-funded project dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants (64).

Genotype/Phenotype Associations

Genotype only occasionally substantially informs management of affected patients. While index cases with pathogenic variants present at younger ages, neither risk of ventricular arrhythmias during follow-up nor prevalence of structural dysfunction differ between gene-positive and gene-elusive ARVC patients. Individuals with multiple pathogenic variants do have earlier-onset disease and a higher risk for malignant ventricular arrhythmias and sudden death (6, 57, 65). Among 577 carriers of desmosomal and *PLN* mutations from ARVC families, the 4% with multiple mutations also had more frequent left ventricular dysfunction, New York Heart Association Class C heart failure (66), and cardiac transplant, suggesting a gene dosage effect in ARVC (6). Another genotype/phenotype association that may guide management is a very high risk of sudden death among male carriers of the founder *TMEM43* variant p.(Ser358Leu) (67). Furthermore, the likelihood of left ventricular involvement varies among carriers of different mutations with biventricular disease, common among patients with *PLN* (68) or *DSP* (69) variants.

Toward Personalized Approaches to Early Detection and Cascade Screening

The clinical utility of genetic sequencing for ARVC is primarily to inform cascade screening for at-risk family members—also an American College of Cardiology/American Heart Association/Heart Rhythm Society Class I recommendation (70). When a definitively pathogenic variant is detected in a proband, relatives who did not inherit it are generally cleared of ongoing cardiac screening, while those who carry the variant are recommended for close surveillance (31). In well-characterized ARVC families, one-third of at-risk relatives will develop definite ARVC. For example, Quarta et al. (11) reported that 34% of first-degree relatives with mutations had a definite diagnosis of ARVC, while another 27% had a borderline diagnosis. Groeneweg et al. (5) reported that 40% of 385 at-risk family members with a pathogenic variant detected via cascade screening met diagnostic criteria.

A key goal of managing genotype-positive at-risk relatives is detecting early signs of disease to prevent sudden cardiac death. A long-standing paradigm suggests three phases of ARVC: (a) the concealed stage, in which patients may have genetic risks and possibly subtle molecular abnormalities but few, if any, abnormalities detectable on conventional cardiac screening; (b) the electrical stage, in which abnormalities may be detected on electrocardiogram (ECG) or Holter monitoring, but conventional imaging shows normal or near-normal structure; and (c) the structural stage, with the full phenotype expressed. Whether patients have an appreciable risk of life-threatening arrhythmias during the concealed and electrical stages is a debated question. Recent evidence suggests that the highest arrhythmic risk occurs with detectable structural disease, and that full phenotypic expression heralds arrhythmic risk (71, 72). However, case series of molecular autopsies have reported ARVC-associated mutations in sudden cardiac death victims with reportedly normal cardiac structure on autopsy (73).

Collaborative research has begun to both answer this question and provide the evidence base needed to develop personalized approaches to familial screening. Te Riele et al. (74) recently investigated outcomes of 274 first-degree relatives of 138 ARVC probands. Ninety-six (35%) were

diagnosed with ARVC, most during initial cascade screening. Presence of cardiac symptoms, a pathogenic mutation, being a sibling, and female sex were predictors of ARVC diagnosis. During seven years of follow-up, 8% of relatives ($n = 21$) experienced a potentially life-threatening ventricular arrhythmia. Each met diagnostic criteria and had both electrical and structural abnormalities before experiencing their arrhythmic event. Electrical abnormalities evident on screening always preceded or were contemporaneous with structural dysfunction. This observation, also seen in other publications (72, 75), supports regular ECG and Holter monitoring as a priority for ongoing clinical surveillance of at-risk family members; in asymptomatic individuals with normal electrical screening, less frequent structural evaluation may be reasonable. Recent data suggest specialized echocardiogram analysis may also be valuable for detecting early phenotypic expression in relatives. Mast et al. (76) showed that normal RV deformation in the subtricuspid region is associated with absence of disease progression during a four-year follow-up in relatives of patients with ARVC. Abnormal right ventricular deformation notably seems to precede other established signs of ARVC. Deformation imaging may thus eventually play an important role in ARVC family screening protocols. Multicenter efforts to enable adequately powered individualized prediction of risks among family members are being planned.

Another question to be addressed in family screening is whether relatives of gene-elusive patients, particularly those with no ARVC family history, should be offered a modified, less aggressive screening algorithm. Most ARVC probands with familial disease have a pathogenic variant (89% in Reference 5), perhaps suggesting that gene-elusive ARVC is less likely to be heritable. Among the 274 first-degree relatives reported by te Riele and colleagues (74), relatives in gene-elusive families were significantly less likely to meet Task Force Criteria, and more importantly sixfold less likely to experience a sustained ventricular arrhythmia ($n = 2$, 1.9% of total gene-elusive family members). These data suggest a lower likelihood of disease in relatives of gene-elusive cases and perhaps less rigor needed in the schedule for ongoing cardiac screening than is appropriate for at-risk carriers from gene-positive families. Evidence suggesting that ARVC in isolated gene-elusive probands may be substantially exercise induced strengthens the rationale for personalizing management of their family members according to the family genotype.

EXERCISE

Physicians have long recognized that their ARVC patients were disproportionately endurance athletes. Sudden cardiac death in ARVC is often precipitated by exercise (7, 77). A review of autopsies from the Veneto region of Italy showed that competitive athletics was associated with a fivefold increase in sudden cardiac death risk among adolescents and young adults with ARVC (78). Implementation of a preparticipation screening program resulted in a sharp decline in these deaths (79).

The discovery that pathogenic variants in the desmosomal genes were associated with ARVC provided a potential explanation for this association. Murine ARVC models, now available for each of the desmosomal proteins, consistently show a cardiovascular phenotype that is induced and/or exacerbated by exercise (80–83). The molecular mechanism underpinning this susceptibility to exercise is an active area of research. There is also emerging evidence of a cohort of athletic ARVC patients without known ARVC mutations who may have a largely exercise-induced form of disease. These cases are characterized by very high levels of athletic activity, no evidence of a pathogenic variant, and an absence of family history of ARVC (61, 84).

Association Between Exercise and Penetrance/Severity in Patients

During the past five years, clinical studies (summarized in **Table 2**) have attempted to more precisely define the influence of exercise on penetrance, arrhythmia risk, and structural progression.

Table 2 Clinical studies of the influence of exercise on patient outcomes

| Reference | <i>n</i> | Population | Methodology | Exercise/athlete definitions | Findings |
|-----------|----------|--|---|---|---|
| 85 | 87 | Pathogenic desmosomal variant carriers | Lifetime exercise interview | Athlete: participant in a sport with a high dynamic demand (>70% maximum O ₂) >50 h in one year at vigorous intensity | Increased penetrance, worse lifetime survival free from sustained ventricular arrhythmias and Class C heart failure in athletes Fewer incident ventricular arrhythmias in those who reduced exercise duration |
| 61 | 82 | Probands with definite ARVC | Lifetime exercise interview Family history | Athlete defined as above Average hours per year MET-hours per year | Gene-elusive nonfamilial ARVC is associated with very-high-intensity exercise All gene-elusive patients were athletes |
| 91 | 37 | Carriers of a <i>PKP2</i> variant from 10 families | Lifetime exercise interview | Athlete defined as above Average hours per year MET-hours per year Exercise relative to AHA target for healthy adults (450–750 MET-min weekly) | Family members restricting exercise to the AHA minimum upper bound less likely to develop ARVC AHA-minimum recommended exercise for healthy adults may be reasonable for unaffected <i>PKP2</i> variant carriers |
| 15 | 88 | ARVC patients with pathogenic variants | Lifetime exercise interview | Athlete defined as above Average hours per year at each age | Patients presenting before age 18 more likely to have been athletes in adolescence than those presenting as adults |
| 84 | 47 | Athletes with complex right ventricular arrhythmias | Clinical interview | Athlete: intensity ≥6 METs, duration ≥4 h/week | Among 41 athletes with definite or probable ARVC, only 6 had a definite or possible desmosomal mutation, and few had a family history of disease Mutation carriers had done significantly less exercise than the remaining cases |
| 86 | 108 | Probands with definite or borderline ARVC | Questionnaire at enrollment | Self-defined inactive, recreational, or competitive athlete before and after diagnosis | Competitive sports associated with higher risk of ventricular arrhythmias/death when compared with both recreational sport and inactive patients No increased risk associated with recreational sports |
| 87 | 110 | 65 ARVC probands and 45 mutation-positive family members | Telephone interview | Athlete: intensity ≥6 METs, duration ≥4 h/week for a minimum 6 years | Athletes among the asymptomatic mutation carriers had lower left ventricular function and more right ventricular abnormalities Athletes had a higher frequency and earlier onset of ventricular arrhythmias Only athletes required transplant |

(Continued)

Table 2 (Continued)

| Reference | <i>n</i> | Population | Methodology | Exercise/athlete definitions | Findings |
|-----------|----------|-------------------------------|--|---|--|
| 16 | 301 | Definite ARVC | Clinical interview; athletes further interviewed For nonathletes, no detailed history | Strenuous exercise: vigorous-intensity physical activities (≥ 6 METs) ≥ 5 h/week for ≥ 1 year | Strenuous exercise after diagnosis was associated with poorer survival from life-threatening arrhythmia |
| 92 | 116 | Definite ARVC (1994 criteria) | Clinical history | Long-term endurance training (equivalent to > 1 marathon per year for > 10 years) | Athletes had increased right and left ventricular volumes, reduced right ventricular function, and more right ventricular abnormalities No differences in ventricular arrhythmias |
| 89 | 173 | Definite ARVC | Interview | Physical activity in the preceding 3 years, median duration per week High intensity: ≥ 6 METs | High-intensity exercise an independent predictor of ventricular arrhythmias even after adjusting for long exercise duration Exercise dose (high and long) was the best predictor of structural dysfunction |
| 88 | 129 | Definite ARVC with ICD | Lifetime exercise interview | Change in exercise from 3 years before diagnosis to after presentation | Greater reduction in exercise dose conferred greater reduction in risk of ventricular arrhythmias Patients without desmosomal mutations and those with primary prevention ICDs benefited more from exercise reduction |

Abbreviations: AHA, American Heart Association; ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; MET, metabolic equivalent; *PKP2*, plakophilin-2 gene.

For patients meeting Task Force Criteria, these studies consistently show that athletic activity both prior to and after ARVC presentation is associated with higher risk of ventricular arrhythmias in follow-up (16, 85–87). Furthermore, reducing the exercise dose (duration \times intensity) significantly reduces the risk of ventricular arrhythmia in follow-up (88, 89). The extent of both right and left ventricular structural dysfunction is also correlated with athletic history (61, 87, 89). While no study has prospectively assessed the effect of exercise reduction on structural progression, athletic activity is associated with poor clinical outcomes; one study found that only athletes progressed to transplant (87), and another reported that only athletes developed Class C heart failure (85). Based on these data, experts in the field and both European and North American professional societies recommend that ARVC patients avoid competitive and high-intensity exercise (31, 70).

The more challenging clinical issue relates to exercise in at-risk family members. There appears to be a dose-dependent relationship between exercise and likelihood of developing ARVC. A study of 87 carriers of heterozygous desmosomal pathogenic variants showed that both participation in vigorous endurance athletics and greater duration of annual exercise were

associated with an increased likelihood of a definite ARVC diagnosis in a dose-dependent fashion (85). Furthermore, genotype-positive ARVC patients with a clinical presentation during adolescence are significantly more likely to have participated in endurance athletics during their youth than are ARVC patients diagnosed as adults (15). Consistent with this, Saberniak et al. (87) found that age of starting athletic training was correlated with age at ICD implantation, suggesting a temporal relationship between timing of exercise exposure and disease onset. This study also illustrated a linear relationship between the amount of physical activity and extent of right and left ventricular dysfunction in both patients and at-risk family members. Additionally, among asymptomatic family members, athletes had worse left ventricular function and more right ventricular abnormalities.

Toward Personalized Exercise Recommendations

How to integrate these data into exercise recommendations for family members remains a challenging question. Presymptomatic genetic testing of at-risk relatives allows not only early diagnosis but also the possibility of decreasing risk of developing ARVC through lifestyle modification, a rare opportunity in a genetic disease. However, exercise is associated with a multitude of health benefits, and limiting exercise is not without risk. We recently assessed the exercise threshold for disease onset based on the American Heart Association (AHA) minimum recommended exercise (90) in members of nine families with *PKP2* variants (91). Family members who restricted exercise at or below the upper bound of the AHA minimum were significantly less likely to be diagnosed and had no sustained ventricular arrhythmias. At diagnosis and first sustained ventricular arrhythmia, they had accumulated 2.8-fold and 3.5-fold, respectively, the AHA-recommended minimum MET-hours of exercise since age 10. (MET stands for metabolic equivalents of task. A MET unit reflects the resting volume of oxygen consumption for a 70 kg man; 1 MET is equivalent to 3.5 mL/min/kg body weight.) A study is under way to confirm that AHA-recommended minimum exercise falls below the threshold to promote disease onset, and also to expand the cohort to include patients with other desmosomal variants.

Another key question is whether exercise restriction is warranted in ARVC patients and at-risk relatives with rarer genotypes, such as in patients with pathogenic founder mutations in *PLN* (54) and *TMEM43* (67). In addition, unaffected family members of gene-elusive probands with a normal initial evaluation may have a considerably lower ~~prior~~ risk of developing ARVC and thus a lesser indication for possible exercise restriction. These populations merit further study.

Studies have also begun to explore whether personalized approaches to exercise can be developed for affected patients. Two recent publications have suggested that reducing exercise dose is ideal (88, 89). Lie et al. (89) further established that while both high intensity and long duration of exercise were associated with ventricular arrhythmias, intensity remained an independent predictor after investigators adjusted for duration, suggesting that reduction in exercise intensity may be particularly important to target. We recently explored whether exercise recommendations could be tailored on the basis of arrhythmia history or genotype (88). We found that among 129 ARVC patients with ICDs, as expected, patients who reduced exercise the most had the lowest risk of ICD therapy in follow-up. As shown in **Figure 2**, top-tertile exercise reduction seemed to confer the greatest benefit to gene-elusive patients and to those who were implanted for primary prevention. While these results await confirmation, they have clinical utility in discussions with patients about the risks and benefits of exercise. How exercise plans can be integrated into risk stratification and shared decision making for ICD implant is also an important question for future research.

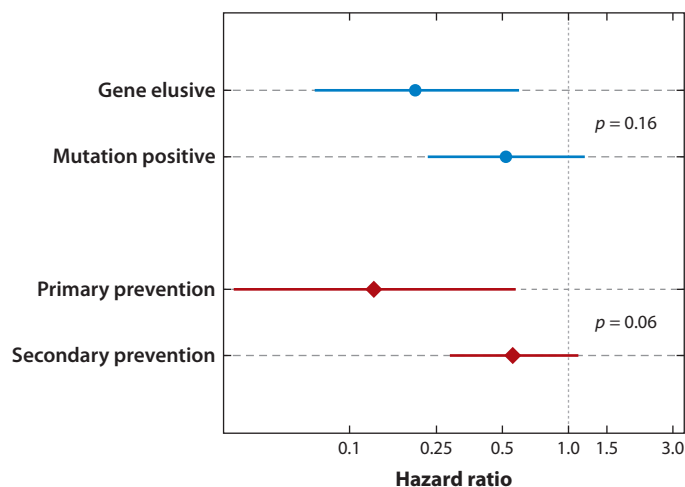


Figure 2

Influence of top-tertile reduction in annual exercise dose (MET-hours) on survival from first appropriate ICD therapy among 129 definite ARVC patients with ICDs stratified by genotype and primary versus secondary prevention. Adjusted hazard ratios are for first appropriate ICD therapy according to reduction in exercise dose stratified by genotype and primary versus secondary prevention. Sex, age at presentation, primary or secondary prevention, mutation, proband status, and annual exercise dose before clinical presentation were each adjusted for. P-values for the interactions are listed. Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; MET, metabolic equivalent. Adapted from Reference 88 with permission.

FUTURE DIRECTIONS

The combined insights gained from natural history studies, improved understanding of pathogenic mechanisms, and appreciation of genetic and environmental modifiers have set the stage for developing personalized approaches to managing both ARVC patients and their at-risk family members. Collaborative research by the ARVC community to enable adequately powered analyses is a key next step so that patients may fully benefit from these advances. Numerous national and regional efforts are already under way. Through harmonizing data collection, building systems to facilitate secure data sharing, and building multidisciplinary teams, the community has the potential to translate the scientific advances of the past decade into evidence-based, personalized care during the next one.

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