Arrhythmogenic Right Ventricular Cardiomyopathy
Toward a Modern Clinical and Genomic Understanding

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Since its first description in the 1700s by the pope’s physician, a professor of anatomy in Rome, the condition known as arrhythmogenic right ventricular cardiomyopathy (ARVC) has resisted attempts at categorization. In 1982, when the first major case series was published in Circulation, Marcus et al described patients with recurrent ventricular tachycardia, RV enlargement, and partially or totally absent RV myocardium replaced instead by fibrofatty tissue. Thought to be a congenital developmental defect of the RV musculature, the condition was classified as a dysplasia. Although this thinking was later revised, the initial observation is memorialized in the hybrid name arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C), still in wide use. In the intervening years, new information about this progressive, hereditary disease has repeatedly forced us to redraw the lines between categories that, for mental clarity, we like to think of as distinct: cardiomyopathy versus arrhythmia syndrome; hereditary versus lifestyle-induced. In this issue of Circulation: Cardiovascular Genetics, 2 leading groups in ARVC research, from Johns Hopkins University and from an interuniversity consortium in The Netherlands, have joined their patient registries to help better define the natural history of this still-perplexing disease. The result is the largest, most comprehensive long-term outcomes study yet—involving 439 ARVC index patients who were followed for a median of 7 years, and 562 of their family members. The results, in line with previous observations, are a valuable contribution.

Clinical Features

The hallmark of this disease is ventricular arrhythmias, which predispose patients to syncope and sudden cardiac death—often during exercise. The first signs of ARVC typically do not appear until adolescence or early adulthood. Disease expression is highly variable, both between and within families, and penetrance is reduced: estimated at perhaps 60% during a lifetime. Even closely related individuals who share the same causative genetic variant may have radically different outcomes. Electrical abnormalities on ECG, Holter monitor, signal-averaged ECG, or exercise treadmill test are among the earliest features of the disease, typically preceding any structural remodeling visible on echocardiogram or MRI. During these early stages, there is nonetheless a substantial risk for sudden death. ARVC has, in this regard, more in common with inherited arrhythmias such as long QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia than with inherited cardiomyopathies, such as hypertrophic cardiomyopathy (HCM).

Groeneweg et al clearly document the large arrhythmia burden associated with ARVC. Of the 439 index patients in their cohort, 11% presented with cardiac arrest at a median age of 25 years. An additional 50% presented with sustained ventricular arrhythmias. Among index patients who entered the study alive, 72% had a life-threatening ventricular arrhythmia during the follow-up period. Largely attributable to implantable cardioverter defibrillators, however, overall cardiac mortality was low (6%). This arrhythmic burden differs markedly from what is seen, for example, in HCM. For patients with HCM in the highest risk groups (ie, given an implantable cardioverter defibrillator), O’Mahony et al report a 5-year cumulative incidence of appropriate shock for ventricular tachycardia/ventricular fibrillation of 13% (12% for primary prevention patients and 20% for secondary prevention). By contrast with arrhythmias, progression to symptomatic heart failure in ARVC index patients occurred in only a minority (13%) during follow-up, with 4% undergoing cardiac transplantation (similar to statistics for HCM).

As the authors note, this is the largest study to use the new, more sensitive 2010 Task Force Criteria for diagnosis. In 1994, an international working group sought to standardize diagnosis of ARVC with the Task Force Criteria, a checklist of major and minor disease criteria spanning ECG abnormalities, arrhythmias, RV structural abnormalities, histopathologic findings, and family history. This complicated system unfortunately lacks the elegance of a QTC interval for long QT syndrome, or an LV wall thickness measurement for HCM; for ARVC, no one clinical test can reliably reveal presence of the disease. Furthermore, it soon became clear that these criteria, developed based on index patients with severe disease presentation, lacked sensitivity for mild disease. By placing more weight on ECG abnormalities, and (in this new molecular era) on the presence of disease-causing genetic variants, the modified 2010 criteria better captured individuals in the earliest stages of the disease.
Exercise Effects

A potential role for exercise in shaping the disease trajectory has been posited for some time. Anecdotal reports from clinicians combined with observations derived from forced exercise in animal models were hypothesis generating.\(^1\) In 2013, more convincing data from an observational study of patients from the Johns Hopkins ARVD/C Registry by James et al\(^1\) supported this idea. Among 87 patients with the genetic predisposition to ARVC, a history of intensive (and particularly endurance) exercise increased the likelihood of developing ARVC. Exercise also increased the likelihood of adverse outcomes, including life-threatening arrhythmias and heart failure. In response to these findings, which have been mirrored by others,\(^1\) the Johns Hopkins group now counsels severe exercise restriction—not just for patients with diagnosed ARVC, but for preclinical mutation carriers as well.\(^1\) (Given substantial variability among individuals, we counsel moderate restriction for all patients and severe restriction only in those with progressive disease.) This differentiates the trend in ARVC-related exercise research from long QT syndrome, for example, for which current debate involves data suggesting we may be over-restricting athletes with the disease.\(^1\)

A challenge posed by exercise limitation guidelines\(^1\) across the spectrum of inherited heart disease is the substantial body of literature supporting dramatic and positive effects of exercise on multisystem disease pathologies. Reconciling these potent reductions in risk, supported by an evidence base of hundreds of thousands of individuals,\(^1\) with the potential reductions in risk implied by studies such as the one by James et al\(^1\) in (by necessity) smaller groups of gene-positive individuals is a challenge faced by our community on a daily basis.

Certainly, these findings highlight the importance of prompt genetic testing for probands, and of cascade genetic testing among family members, so that individuals at known risk can be better protected. At the same time, they again force us to reconsider how we classify this disease: as an inexorable process controlled by heredity, or one under the control of specific lifestyle choices? One irony of the exercise data is that a disease prompting a recommendation of exercise restriction may be more likely to strike those with an intensive dedication to, and love of, sports.

Genetic Underpinnings

In 2002, the first gene responsible for autosomal-dominant ARVC was reported: DSP, coding for the protein desmoplakin.\(^1\) It forms part of the desmosome, a transmembrane protein complex that provides mechanical cell–cell adhesion between cardiomyocytes. In rapid succession, 4 other desmosomal genes were implicated: PKP2 (plakophilin-2), DSG2 (desmoglein-2), DSC2 (desmocollin-2), and JUP (plakoglobin). Nondesmosomal genes (TMEM43, PLN, and others) have been implicated as well. The condition rapidly became known as a disease of the desmosome: so much so that Asimaki et al\(^2\) in the New England Journal of Medicine proposed a new diagnostic test based on reduced immunostaining of plakoglobin at myocardial cell–cell junctions.

With this new genetic understanding came surprising evidence for an overlap between ARVC and other hereditary cardiac conditions, generally thought to be distinct—starting with dilated cardiomyopathy. Previously, investigations at autopsy had revealed the fibrofatty histopathology of ARVC exclusively in the left ventricles of some patients with sudden cardiac death.\(^3\) The possibility of a left-dominant form confounded prevailing notions of a purely right-sided, or at most biventricular, disease. With the advent of genetic testing, however, it became clear that this left-sided form, routinely mistaken for dilated cardiomyopathy, was also caused by desmosome gene variants: often in DSP.\(^3\) They were in fact the same disease. For this reason, Sen-Chowdhry et al\(^4\) endorse a more ventricle–neutral name for the condition: arrhythmogenic cardiomyopathy.

Compared with previous studies, Groeneweg et al\(^5\) report a robust yield for genetic testing in their cohort: 63% of the 439 ARVC index patients tested positive for a presumed disease-causing variant in PKP2, DSP, DSG2, DSC2, JUP, TMEM43, or PLN. This is higher than previous yield estimates of ≈40% to 50%, made shortly after desmosome gene sequencing first became available.\(^1\) It is worth noting that almost 50% of the gene-positive families in this cohort carry one of the founder mutations common in The Netherlands, however. The yield also received a boost from the PLN gene, which is reported to be causative in 5% of the families and has not been sequenced in many other cohorts. Still, the overall yield is on par with the 58% of ARVC families (and 73% of living probands) reported to be gene-positive by Quarta et al\(^6\) in a British cohort.

Perhaps the most striking finding involves the impact of family history on genetic testing yield. Among the 295 index patients with familial ARVC, 89% had an identifiable mutation. This is similar to findings for HCM. In an Australian cohort, for example, Ingles et al\(^7\) reported a testing yield of 72% for HCM probands with affected relatives, and only 29% for those without.

A central challenge for the field of ARVC research remains tackling the ≈40% of cases for which a genetic cause remains elusive. Some small percentage of cases will certainly be solved with more routine addition of structural variant testing for deletions, duplications, and rearrangements involving desmosomal genes. Other cases may involve desmosome-associated candidate genes, some of which are currently being investigated,\(^8\) or upstream regulators of gene expression and protein trafficking.

Yet with such a large percentage of ARVC still unexplained at the molecular level, it is worth asking whether patients without identifiable desmosome gene variants really have the same disease. Based purely on the phenotype of the 2 groups, Groeneweg et al’s\(^8\) answer to this question is yes. They report that clinical characteristics and disease outcomes were similar in index patients with and without identifiable genetic variants, including rates of sustained ventricular tachycardia and ventricular fibrillation. There was 1 notable exception: probands with identifiable gene mutations had their first onset of symptoms, and first sustained ventricular arrhythmia, at a significantly younger average age than the gene-elusive probands (a difference of 4 years).

The authors suggest that their findings help to clarify the question of exercise-induced RV cardiomyopathy, proposed by Heidbuchel et al.\(^9\) This entity, distinct from ARVC and with more benign outcomes, is a more profound athlete’s heart; among ultra-elite athletes, the higher end-systolic wall stress experienced by the right versus the left ventricle may be extreme enough to break down even healthy desmosomes, with arrhythmogenic consequences. A stated goal of this article was...
to provide insight into whether isolated ARVC cases (with no family history and no discernable genetic cause) might represent such an acquired entity. In their discussion, Groeneweg et al stated that they found no evidence for 2 different conditions in their cohort. Specifically, between patients with familial versus seemingly isolated disease, there were no clinically significant differences in sustained ventricular arrhythmias, ECG abnormalities, structural and functional abnormalities, or heart failure. However, although many remain to be convinced about the entity of exercise-induced RV cardiomyopathy as described by Heidbüchel et al, this article cannot reasonably be held to offer much to this debate because these authors report no data on exercise burden in their subjects, nor do they suggest any were high level athletes of the type described by Heidbüchel et al.

**Molecular and Phenotypic Overlap**

Some of the most fascinating recent work on the molecular basis of this disease involves the unexpected overlap between ARVC and Brugada syndrome. Similar to the finding that defects in the ion channel gene SCN5A can cause dilated cardiomyopathy, these results alert us that our previously clean boundaries between the channelopathies and the cardiomyopathies no longer apply. Desmosomes, after all, do not exist in isolation; they cluster at the junctions between cardiomyocytes, within the intercalated disk. Multiple studies have shown that when desmosomes are disrupted, this impacts other molecules colocalized at those disks—among them Na1.5, the major protein component of the voltage-gated cardiac sodium channel. SCN5A, the gene that codes for Na1.5, is a major player in Brugada syndrome; variants in this gene are considered responsible for ≈25% of the disease, via reduced sodium channel function. There is some evidence that defects in the desmosome may have a similar effect. In vitro studies have demonstrated a sodium current deficit in human induced pluripotent stem cell–derived cardiomyocytes from an ARVC patient with variation in PKP2. Furthermore, PKP2 variants capable of dampening sodium current in vitro have been found in patients diagnosed with Brugada syndrome. Meanwhile, immunostaining studies have also shown a decrease in gap junction proteins (connexin-43) at the intercalated disks in heart tissue from patients with ARVC. By electrically uncoupling neighboring myocytes, loss of gap junctions is thought to disrupt the electrical integrity of the myocardium, slowing conduction and predisposing to arrhythmias. As a result, ARVC is newly understood as a disease associated not just with dysfunction at the desmosome, but at the entire intercalated disk.

This increasing overlap between inherited cardiovascular conditions at both a phenotypic and molecular level creates a certain humility about our ability to distinguish one disease from another along a phenotypic spectrum. To compensate, a tempting approach is to use the most comprehensive gene panel possible for diagnostic testing—even if most genes on the panel do not seem to apply to the patient’s phenotype. This is indeed the trend among clinical testing laboratories, which now offer pancardiomyopathy, pan-arrhythmia, or even pan-cardiology panels with many dozens of genes. Ironically, ARVC is also the disease that makes the most convincing argument against overly broad sequencing: As the number of genes tested expands, so do the number of variants of unknown significance detected. The genes that underlie ARVC are now notorious for their high rate of background variation, even among presumably healthy individuals from the general population. Kapplinger et al reported the most sobering statistic: ≤16% of presumably healthy controls may have a rare missense variant in one of the ARVC susceptibility genes. Given a disease prevalence of 1:1000 to 1:5000, it is clear that most of these variants cannot be disease causing.

Careful variant interpretation is of the utmost importance, therefore, before concluding that a rare variant is pathogenic. This raises concern that some missense variants classified as disease causing by Groeneweg et al could in fact be benign, muddying the distinction between gene-positive and gene-negative families. The authors’ criteria for classifying a missense variant as pathogenic are decidedly weak, based only on rarity in the National Heart, Lung, and Blood Institute’s Exome Sequencing Project (minor allele frequency ≤0.05%) and agreement between 2 in silico prediction algorithms (criteria not sufficient under current American College of Medical Genetics and Genomics guidelines). It is reassuring, therefore, that among the gene-positive families <10% have a single rare missense variant listed as their pathogenic mutation, once a well-characterized Dutch founder mutation in PKP2 (p.Cys796Arg) is excluded. The vast majority instead carry radical variants (nonsense, frameshift, splice-site, or single-codon deletion), confidently believed to cause disease.

**Moving Forward**

As we look to the future, what can be done to improve disease outcomes? In this era of genetic testing, a growing population of gene-positive individuals exists who are at known risk for ARVC but not yet showing clinical features of disease. Currently, gene-positive children can be steered away from competitive sports before these become central to their identities and social lives—with the hope of reducing both penetrance and severity of disease. For families without identifiable mutations, the difficulty of diagnosing ARVC at its earliest stages remains a concern, given that 20% to 50% of index patients present with sudden cardiac death as the first sign. The frequency of life-threatening arrhythmias as a first presentation underscores the importance of prompt cardiology screening for at-risk family members, and sensitivity to signs and symptoms of disease that may precede an official diagnosis. What is still lacking, however, is a reliable algorithm for risk assessment that can predict an individual patient’s chances of developing life-threatening arrhythmias, and guide decision making about prophylactic implantable cardioverter defibrillator placement (such as the methods that exist for HCM).

The ultimate goal, of course, is to slow or even reverse progression of the disease. In this regard, recent work by Asimaki et al involving high-throughput chemical screening in a zebrafish model of ARVC, shows early promise. So do insights from Marian’s group involving the role of cardiac progenitor cells and canonical Wnt signaling in the disease. Among carriers of Dutch founder mutations, the shared genetic substrate may be fertile ground for insights into additional modifier genes and molecular pathways that influence disease outcome. Although much remains to be learned about the boundaries of arrhythmogenic cardiomyopathy, how broadly to look for genetic causes, and how to counsel both our patients and their families, this study adds substantially...
to our understanding and clearly articulates a path forward for future studies.

**Disclosures**

Dr Ashley is a founder of and advisor to Personalis, Inc. K. Dunn is a member of Invitae’s Cardiology Advisory Board.

**References**


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