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Arrhythmogenic right ventricular dysplasia/cardiomyopathy: Clinical challenges in a changing disease spectrum

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ABSTRACT

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by fibro-fatty replacement of predominantly the right ventricle (RV), which predisposes patients to life-threatening ventricular arrhythmias and usually slowly progressive ventricular dysfunction. The disease is inherited as an autosomal dominant trait with incomplete penetrance and variable expressivity. Increased appreciation of ARVD/C as a "disease of the desmosome" has fueled research into possible disease mechanisms, and insights into ARVD/C pathogenesis are rapidly advancing. Although ARVD/C is known to preferentially affect the RV, early and/or predominant left ventricular involvement is increasingly recognized. Diagnosis is made by combining multiple sources of diagnostic information as prescribed by the consensus-based Task Force criteria. Affected individuals typically present in the third to fifth decade of life with palpitations, lightheadedness, or syncope due to frequent ventricular ectopy or arrhythmias originating from the RV. However, disease expression is highly variable, even among subjects from the same family or those carrying the same mutation. Since sudden cardiac death can be the first manifestation of the disease, optimizing the approach to early detection and risk stratification of ARVD/C is of utmost importance. This review will discuss the changing spectrum of ARVD/C based on recent advances in diagnosis, genetics, and improved understanding of disease pathophysiology.

Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), also known as arrhythmogenic cardiomyopathy, is one of the most arrhythmogenic forms of inherited cardiomyopathy and a cause of sudden cardiac death (SCD) in the young. The disease is characterized by fibro-fatty replacement of predominantly the right ventricle (RV), which predisposes patients to life-threatening ventricular arrhythmias and slowly progressive ventricular dysfunction [1]. In ARVD/C, RV disease usually predominates, although early and predominant left ventricular (LV) involvement is increasingly recognized [2]. The last decade has witnessed the identification of pathogenic ARVD/C-causing mutations in five desmosomal genes and several non-desmosomal genes in up to 60% of index patients [3]. This fueled investigations into disease mechanisms of ARVD/C and led to our current understanding of ARVD/C as predominantly a "disease of the desmosome."

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ARVD/C patients typically present in the third to fifth decade of life with stable monomorphic ventricular tachycardia (VT) originating from the RV, which is caused by heterogeneous myocardial tissue alteration giving rise to reentry circuits. However, current data suggest that electrical abnormalities often precede detectable structural remodeling of the myocardium [4]. As such, early detection and risk stratification of ARVD/C are of utmost importance.

This review will provide an overview of ARVD/C diagnosis, genetics, pathophysiology, and treatment. We will discuss the changing spectrum of ARVD/C based on recent advances in the field, with a focus on distinguishing ARVD/C from other cardiomyopathies, early disease detection, and arrhythmic risk stratification.

ARVD/C in a historical perspective

The first description of ARVD/C is believed to date back to 1736, when Giovanni Maria Lancisi reported on a family with heart disease recurrence in four generations. In his book "*De Motu Cordis et Aneurysmatibus*," Dr. Lancisi described a family with palpitations, heart failure, RV aneurysms, and SCD in multiple family members [5]. However, it was not until 1982 that the first comprehensive clinical description of ARVD/C was published. In their seminal article, Marcus et al. [1] reported on 24 patients with arrhythmias of RV origin and RV enlargement. Because the underlying pathophysiology was thought to be a developmental defect of the RV myocardium, the disease was initially considered a "dysplasia." The developmental abnormalities were thought to preferentially involve the RV inflow tract, RV outflow tract, and apex, collectively called the "Triangle of Dysplasia." Evidence would subsequently show, however, that ARVD/C is not a defect present at birth but rather an acquired and progressive disease. This has evolved in our current understanding of ARVD/C as a genetically determined cardiomyopathy.

Clinical presentation

ARVD/C has an estimated prevalence of 1 in 1000 to 1 in 5000 Caucasian individuals, although some studies report that the real prevalence could be higher due to under-recognition [6]. Affected subjects typically present in the third to fifth decade of life with palpitations, lightheadedness, or syncope due to frequent ventricular ectopy or arrhythmias originating from the RV. It is extremely rare to manifest clinical signs or symptoms of ARVD/C before the age of 12 years or after the age of 60 years. However, it is important to note that disease expression is highly variable between patients, even among those from the same family or those carrying the same mutation. Unfortunately, SCD may be the first clinical manifestation of ARVD/C in a subset of index cases, predominantly young and athletic individuals [4,7,8].

Advances in molecular genetics

Although a familial basis of disease was suspected since the first report, it was only in the last decade that the genetic basis of ARVD/C was elucidated. The seminal discovery of mutations in junction plakoglobin in 2000 in individuals with Naxos disease, an autosomal recessive cardio-cutaneous syndrome with ARVD/C, directed further research into the genetic substrate of ARVD/C to other genes encoding desmosomal proteins [9]. This approach identified mutations in four additional desmosomal proteins causing or contributing to ARVD/C: plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), and desmocollin (*DSC*) [3]. In addition, mutations in several non-desmosomal genes have also been reported to cause ARVD/C: transmembrane protein-43 (*TMEM43*), desmin (*DES*), titin (*TTN*), transforming growth factor beta-3 (*TGFB3*), and phospholamban (*PLN*) [3]. In North America and the Netherlands, mutations in *PKP2* are found in approximately 50% of ARVD/C index patients [10,11], while *PKP2* mutations are less prevalent in other series including the Italian and British cohorts (34% and 36%, respectively) [4,12]. In addition, a *PLN* founder mutation (R14del) has been found in 13% of affected subjects in the Netherlands, thereby being the single most common ARVD/C mutation in this country [13]. In contrast, mutations in *DSP* are much more prevalent in the United Kingdom and in Italy [2,12].

Clinical application of genetic testing in ARVD/C

With the identification of ARVD/C-causing mutations, integration of genetic testing into clinical practice is now proliferating. Currently, its main applications are confirmatory testing in index patients and cascade screening of families. ARVD/C usually has an autosomal dominant inheritance pattern, with incomplete penetrance and variable expressivity. As such, there is considerable phenotypic variability between mutation carriers. It is important to realize that assessing pathogenicity of genetic variants is challenging and should be done with knowledge of the background "genetic noise" in a healthy population [14]. In their important article, Kapplinger et al. [14] highlighted that desmosomal gene mutations, especially rare missense variants, should be interpreted in the context of race and ethnicity, mutation location, and sequence conservation. A large database of genes and mutations underlying ARVD/C has become publicly available (http://www.arvcdatabase.info), which currently contains information of about 900 genetic variants.

Advances in genetic testing

Over the last few years, major progress in next-generation sequencing (NGS) has revolutionized the approach to genetic testing. Rapidly decreasing costs of NGS allows for cost-effective sequencing of the entire genome, including non-coding and regulatory regions [15]. NGS has recently been shown to be successful in identifying novel causative mutations and epigenetic profiling at low cost and with rapid turnaround [16]. Despite the technological advances, data analysis and interpretation may be challenging. In the not-too-distant future, this fast-moving area of NGS research is likely to provide more insights into the genetic aspects of various cardiomyopathies including ARVD/C.