Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia
Clinical Impact of Molecular Genetic Studies

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited heart muscle disease that predominantly affects the right ventricle (RV). It is characterized pathologically by RV myocardial atrophy with fibrofatty replacement and clinically by ventricular electric instability with ventricular tachycardia or ventricular fibrillation that may lead to sudden death, primarily in young people and athletes.1 Later in the disease evolution, progression of RV muscle disease and left ventricular involvement may result in heart failure. The condition was initially believed to be a developmental defect of the RV myocardium, leading to the original designation of “dysplasia.” This concept has evolved over the last 25 years into the current perspective of a genetically determined “cardiomyopathy.” This concept has evolved over the last 25 years into the current perspective of a genetically determined “cardiomyopathy.”

Clinical diagnosis of ARVC/D is often difficult because of the nonspecific nature of disease features and the broad spectrum of phenotypic manifestations. The advent of the molecular genetic era has provided new insights in understanding the pathophysiology of ARVC/D, showing that it is a desmosomal disease resulting from defective cell adhesion proteins such as plakoglobin, desmoplakin, plakophilin-2, and desmoglein-2.1,2,4-7 The availability of molecular testing for mutation screening of disease genes offers the possibility to identify genetically affected individuals. Potential clinical impact of genotype determination includes diagnosis (family screening and preclinical diagnosis); prediction of clinical phenotype (penetrance, gene-specific clinical manifestations); risk stratification (assessment of malignant versus benign mutations); clinical and genetic counseling (restriction of physical activity, family planning); and therapy (prevention of sudden death by implantable cardioverter/defibrillator [ICD]).

Articles p 1641 and p 1650

In this issue of Circulation, studies by Dalal et al5 in the United States and van Tintelen et al6 in the Netherlands address the prevalence and clinical expression of mutations in the plakophilin-2 gene (PKP2) in ARVC/D patient populations of comparable size and fulfilling the task force diagnostic criteria. On both sides of the ocean, a defective PKP2 gene appears to be a major cause of ARVC/D with a prevalence of mutations among unrelated index cases as high as 43% (a figure curiously identical in both studies). In the Dutch study, PKP2 mutations were distinctively identified in ARVC/D probands with familial disease (16 of 23; 70%); no PKP2 mutations were found in patients with an apparently “sporadic” phenotype (0 of 16; \( P<0.001 \)). In both studies there were no significant differences with regard to clinical characteristics and events during follow-up between PKP2 mutation–positive probands and those in whom no mutation was identified. These findings deserve careful consideration because they may remarkably affect our diagnostic approach to ARVC/D, given the concrete possibility of preclinical identification of genetically affected individuals. On the other hand, they point out the limited value of molecular genetic analysis for predicting clinical phenotype and risk of sudden death.

Genetics and Pathophysiology

The estimated prevalence of ARVC/D in the general population ranges from 1 in 2000 to 1 in 5000. The disease affects men more frequently than women, with an approximate ratio of 3:1. A familial background has been demonstrated in >50% of ARVC/D cases. The disease is usually inherited as an autosomal dominant trait with incomplete penetrance and variable expression. The first chromosomal locus (14q23-q24) was published in 1994 after clinical evaluation of a large Italian family. Subsequently, linkage analysis provided evidence for genetic heterogeneity with sequential discovery of several ARVC/D loci on chromosomes 1, 2, 3, 6, 10, 12, and 14. An autosomal recessive variant of ARVC/D (so-called Naxos disease) in which there is a cosegregation of cardiac (ARVC/D), skin (palmoplantar keratosis), and hair (woolly hair) abnormalities has been mapped on chromosome 17 (locus 17q21). The first disease-causing gene, the JUP gene, was identified by McKoy and colleagues4 in patients with Naxos disease. The gene encodes the desmosomal protein plakoglobin, a major constituent of cell adhesion junction. Its discovery suggested that ARVC/D is a cell-to-cell junction disease and stimulated the research in other related genes. Desmoplakin gene (DSP) was the first desmosomal protein gene to be associated with the more common autosomal dominant form of ARVC/D by Rampazzo et al5. Gerull et al6 identified 25 different mutations in the gene encoding plakophilin-2 (PKP2). Most recently, desmoglein-2 gene (DSG-2) mutations have been found in 10% of ARVC/D patients.
unrelated probands. This consistent type of protein alteration supports the concept of “final common pathway” of genetically determined cardiomyopathies, ARVC/D being deemed a desmosomal disease, hypertrophic cardiomyopathy a sarcomeric disease, and dilated cardiomyopathy a cytoskeletal disease, with some exceptions.

Autosomal dominant ARVC/D has been linked to other genes unrelated to cell adhesion complex, such as the gene encoding for cardiac ryanodine receptor (RyR2), which is responsible for calcium release from the sarcoplasmic reticulum, and the transforming growth factor-β3 gene (TGFβ3), which regulates the production of extracellular matrix components and modulates expression of genes encoding desmosomal proteins.

How the mutations of PKP2 gene and more broadly of desmosomal protein genes cause disease remains to be elucidated. It has been hypothesized that the lack of normal protein or the incorporation of mutant protein into cardiac desmosomes may provoke detachment of myocytes at the intercalated discs, particularly under condition of mechanical stress (like that occurring during competitive sports activity). As a consequence, there is a progressive myocyte death with subsequent repair by fibrofatty replacement. Life-threatening ventricular arrhythmias may occur either during the “hot phase” of myocyte death as abrupt ventricular fibrillation or later in the form of scar-related macro-reentrant ventricular tachycardia.

Clinical Diagnosis

The discovery of gene mutations involved in the pathogenesis of ARVC/D has raised the possibility of molecular genetic diagnosis of ARVC/D in clinical care. PKP2 mutations have been associated with the disease frequently. Gerull et al first reported a 27% prevalence of PKP2 mutations among unrelated probands with ARVC/D. The 2 new reports by Dalal et al and Van Tintelen et al confirm and extend these previous observations by showing that PKP2 gene mutations are commonly found in ARVC/D patients, accounting for >40% of the cases. Furthermore, the Dutch study indicates that in familial ARVC/D even the large majority (70%) is caused by PKP2 mutations. A lower prevalence of mutant PKP2 gene has been reported by the studies of Syrris et al and Pilichou et al (11% and 16%, respectively). This discrepancy may be explained by geographic factors, small sample size, and patient selection bias. A potential limitation of both new reports is that patients not carrying PKP2 mutation might have mutations in other ARVC/D-related genes that have not been screened. In a very recent Italian series of 80 unrelated ARVC/D probands undergoing genetic screening of all known ARVC/D genes, 13 (16%) carried a DSP mutation, 11 (14%) a PKP2 mutation, 8 (10%) a DSG2 mutation, and 2 (2.5%) a TGFβ3 mutation. According to previous and new results, molecular genetic diagnosis of ARVC/D appears to be feasible in a significant proportion of patients by screening for mutations in the PKP2 gene and more broadly in desmosomal protein genes.

Task Force Diagnostic Criteria

According to standardized diagnostic criteria proposed by an international task force (Table), the diagnosis of ARVC/D is currently based on the presence of major and minor criteria encompassing ECG, arrhythmic, RV morphofunctional, histopathological, and clinical genetic factors. The diagnosis of ARVC/D is achieved in the presence of 2 major criteria or 1 major plus 2 minor or 4 minor criteria from different groups. Although task force guidelines during the last decade have represented a useful clinical approach to ARVC/D diagnosis, revisions have been proposed to increase sensitivity, partic-

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<table>
<thead>
<tr>
<th>Criteria for Clinical Diagnosis of ARVC/D</th>
<th>Major</th>
<th>Minor</th>
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<tbody>
<tr>
<td>Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
<td>Family history of premature sudden death (age &lt;35 y) due to suspected ARVD/C; family history (clinical diagnosis based on present criteria)</td>
</tr>
<tr>
<td>ECG depolarization/conduction abnormalities</td>
<td>Epsilon waves or localized prolongation (&gt;110 ms) of QRS complex in right precordial leads (V1 to V6)</td>
<td>Late potentials on signal-averaged ECG</td>
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<tr>
<td>ECG repolarization abnormalities</td>
<td>Inverted T waves in right precordial leads (V1 and V6) in people aged &gt;12 y and in absence of right bundle branch block</td>
<td>Sustained or nonsustained left bundle branch block–type ventricular tachycardia documented on ECG or Holter monitoring or during exercise testing; frequent ventricular extrasystoles (&gt;1000/24 h on Holter monitoring)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Severe dilatation and reduction of RV ejection fraction with no or mild LV involvement; localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging); severe segmental dilatation of RV</td>
<td>Mild global RV dilatation or ejection fraction reduction with normal LV; mild segmental dilatation of RV; regional RV hypokinesia</td>
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<tr>
<td>Global or regional dysfunction and structural alterations</td>
<td>Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
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LV indicates left ventricular. Modified from Corrado et al, with permission.
ularly in the context of family screening because of incomplete disease expression. Genetic testing may represent the gold standard on which clinical diagnostic criteria can be compared. The findings of the 2 new studies support the diagnostic accuracy of current task force criteria, given that PKP2 mutations were identified in none of 12 (US study)\(^a\) and in only 2 of 40 (Dutch study)\(^a\) patients not fulfilling diagnostic criteria. Syrris et al\(^b\) reported that the use of modified criteria expanded the diagnostic yield, but it also led to false-positives, ie, family members assumed to be clinically affected but subsequently found to be gene negative. The results of previous and new studies highlight the advantages of a molecular diagnosis of ARVC/D and support the need for a revision of task force guidelines to include molecular genetic information in the family history criteria.

The major task of molecular genetic screening is to achieve a preclinical diagnosis of ARVC/D, which would be particularly useful in family members with incomplete disease expression or in patients with early/minor clinical phenotype. It is important to remember that molecular genetic testing may only support a clinical overt or suspicious diagnosis but cannot make a clinical diagnosis of ARVC/D itself. In fact, mutation carriers may either have no disease phenotype (incomplete penetrance) or present with various degree of clinical manifestations, ranging from asymptomatic family members with concealed RV structural abnormalities and no arrhythmias to patients experiencing cardiac arrest or undergoing cardiac transplantation because of right or biventricular heart failure (variable clinical expression). Inheriting a mutation does not mean that the individual will present clinical manifestation of disease: healthy mutation carriers have only inherited the risk for developing the clinical phenotype. The results of both the US\(^a\) and European\(^a\) studies are in agreement with those of previous investigations of genotype-phenotype correlation that documented a large heterogeneity in clinical expression, as a consequence not only of different desmosomal protein genes but also of different mutations within the same gene. Moreover, Syrris et al\(^b\) recently reported that strikingly different phenotypes can be observed among individuals sharing the same PKP2 gene mutation within the same family. This suggests that other genetic and environmental factors influence clinical expression.

Taken together, these findings suggest that a positive genetic result can only be part of a more comprehensive clinical approach combining multiple sources of diagnostic information such as ECG, arrhythmic, morphofunctional, histopathological, and clinical/molecular genetic findings.

**Risk Stratification and Therapy**

In both new studies,\(^a,b\) the comparison of clinical characteristics of PKP2 mutation carrier and noncarrier ARVC/D patients failed to identify a PKP2-specific clinical phenotype. No significant differences were found with regard to a series of clinical, ECG, and arrhythmic variables between the 2 groups, except for earlier clinical presentation (in the US study)\(^a\) and more prevalent right precordial repolarization abnormalities (in the Dutch study)\(^a\) among PKP2-positive individuals. In addition, in both studies the proportion of patients who received an ICD and the incidence of appropriate discharges during the follow-up did not differ between mutation-positive and mutation-negative probands, suggesting that genetic screening for PKP2 gene mutations is unlikely to contribute significantly to risk assessment. These findings are in agreement with those of genotype-phenotype correlations in other cardiomyopathies, in which genotyping has not been shown to be able to predict phenotype or prognosis on the basis of characterization of malignant versus benign mutations.

The most important aim of genotyping families with ARVC/D is to identify genetically affected relatives before a malignant clinical phenotype and life-threatening ventricular arrhythmias occur. Clinical manifestations of ARVC/D usually develop during adolescence or young adulthood and are preceded by a long preclinical phase. Cardiac arrest may occur in previously asymptomatic young adults and competitive athletes as the first manifestation of disease. Young age is the most powerful independent predictor of ventricular fibrillation in patients with ARVC/D.\(^c\) All efforts should be made to genotype and manage younger family members with ARVC/D who carry the highest risk of sudden death. These efforts are justified by the recognition that timely therapy with ICD provides life-saving protection.\(^d\) Our experience during the past decade showed the favorable clinical outcome (0.08 annual mortality rate) of a large cohort of patients diagnosed with familial ARVC/D who underwent close follow-up and treatment.\(^e\) These findings underscore the importance of early diagnosis of ARVC/D by molecular genetic analysis to establish a focused prevention strategy based on lifestyle modifications (restriction from competitive sports), clinical follow-up (identification of alarming symptoms, ECG/echocardiographic abnormalities, and ventricular arrhythmias), and prophylactic therapy (β-blockers, amiodarone, and ICD) to prevent sudden death.

**Disclosures**

None.

**References**


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