Arrhythmogenic Right Ventricular Cardiomyopathy

A Guide for Clinicians
Arrhythmogenic Right Ventricular Cardiomyopathy

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia (ARVD), is a potentially life-threatening disease that can cause sudden cardiac death in young persons and athletes. ARVC is a disorder of the cardiac desmosome – protein complexes that maintain cell-to-cell connections and provide mechanical attachments among adjacent cells. Myocyte death and replacement by fat and fibrous tissue in the right ventricle are the pathologic hallmark of the disease (Figure 1).

ARVC is an autosomal-dominant genetic disorder. Mutations in a number of genes coding for desmosomal proteins have been associated with ARVC (Table 2). Within families with ARVC, not all mutation carriers will express symptoms, and the age of onset and severity of symptoms may differ greatly within the family. The mutation for ARVC is transmitted equally to men and women, but men are more likely to be symptomatic. ARVC occurs worldwide, and regional differences in frequency have been observed. The disease prevalence is estimated at 1:1000 to 1:2500 but may be higher in certain populations and because of undiagnosed or misdiagnosed cases.¹,²

Clinical Presentation/Course

ARVC patients usually develop symptoms between the second and fifth decades of life. Patients with ARVC typically initially present because of ventricular arrhythmias. The ventricular arrhythmias, which originate in the right ventricle, may be asymptomatic and detected by routine electrocardiogram (ECG) or may cause palpitations, syncope, or sudden death.² The latter stages of the disease are associated with right and even biventricular heart failure.

Standardized diagnostic criteria have been proposed and recently revised (Table 1) in order to enhance sensitivity and improve diagnosis and management.³

Figure 1. Typical histologic features of ARVC. Ongoing myocyte death (a) with early fibrosis and adipocyte infiltration (b).²
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA</th>
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</table>
| **Global or regional dysfunction and structural alterations** | **By 2D echo:**  
- Regional RV akinesia, dyskinesia, or aneurysm  
- and 1 of the following (end diastole):  
  - PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m²)  
  - PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m²)  
  - or fractional area change ≤33%  
**By MRI:**  
- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction  
- and 1 of the following:  
  - Ratio of RV end-diastolic volume to BSA ≥110 mL/m² (male) or ≥100 mL/m² (female)  
  - or RV ejection fraction >40% to ≤45%  
**By RV angiography:**  
- Regional RV akinesia, dyskinesia, or aneurysm | **By 2D echo:**  
- Regional RV akinesia or dyskinesia  
- and 1 of the following (end diastole):  
  - PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m²)  
  - PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m²)  
  - or fractional area change >33% to ≤40%  
**By MRI:**  
- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction  
- and 1 of the following:  
  - Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m² (male) or ≥90 to <100 mL/m² (female)  
  - or RV ejection fraction >40% to ≤45% |
| **Tissue characterization of wall** | • Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy | • Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy |
| **Repolarization abnormalities** | • Inverted T waves in right precordial leads (V₁, V₂, and V₃) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms) | • Inverted T waves in leads V₁ and V₂ in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V₄, V₅, or V₆  
• Inverted T waves in leads V₁, V₂, V₃, and V₆ in individuals >14 years of age in the presence of complete right bundle-branch block |
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<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA</th>
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<tr>
<td>Depolarization/conduction abnormalities</td>
<td>• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V₁ to V₃)</td>
<td>• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG</td>
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<td>• Filtered QRS duration (fQRS) ≥114 ms</td>
<td>• Duration of terminal QRS &lt;40 μV (low-amplitude signal duration) ≥38 ms</td>
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<tr>
<td></td>
<td>• Duration of terminal QRS &lt;40 μV (low-amplitude signal duration) ≥38 ms</td>
<td>• Root-mean-square voltage of terminal 40 ms ≤20 μV</td>
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<td>• Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R’, in V₁, V₂, or V₃, in the absence of complete right bundle-branch block</td>
<td>• Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R’, in V₁, V₂, or V₃, in the absence of complete right bundle-branch block</td>
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<td>Arrhythmias</td>
<td>• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)</td>
<td>• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis</td>
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<td>• &gt;500 ventricular extrasystoles per 24 hours (Holter)</td>
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<td>Family history</td>
<td>• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria</td>
<td>• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria</td>
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<td>• ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative</td>
<td>• Premature sudden death (&lt;35 years of age) due to suspected ARVC/D in a first-degree relative</td>
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<td>• Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation</td>
<td>• ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative</td>
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A patient must have two major, one major and two minor, or four minor criteria from different categories to meet the diagnosis of ARVC. For borderline cases, a patient must have one major and one minor or three minor criteria from different categories. For possible cases, a patient must have one major or two minor criteria from different categories.
The strategy for clinical diagnosis is a combination of multiple sources of diagnostic information, such as genetic, electrophysiologic, anatomic, functional, and histopathologic findings. There are major and minor clinical diagnostic criteria for ARVC (Table 1). Genetic testing can identify presymptomatic individuals within families with ARVC.

ARVC is caused by defects in the components of the cardiac desmosome, intercellular structures that anchor intermediate filaments to the cytoplasmic membrane in adjoining cells. The links form a supportive network in healthy cells. Desmosome protein complexes are found in tissues that experience shear stress, such as heart muscle and epithelium.

Figure 2. In a 17-year-old asymptomatic male athlete who died suddenly during a soccer game, 12-lead ECG showed inverted T waves up to V4 (a) and isolated premature ventricular beats (b). In vitro MRI (c) and corresponding cross section of the heart (d) show RV dilatation with anterior and posterior aneurysms.²
Management

Once a diagnosis of ARVC or genetic susceptibility to ARVC has been established, the main management decision is ICD placement to prevent sudden death. Due to the variable expressivity of ARVC, prognosis is difficult to accurately predict. ARVC patients who are at the highest risk for arrhythmic death include those with a history of having been resuscitated from SCD, those with syncope, those with recurrent sustained arrhythmias and those who have marked right ventricular involvement. The presence of left ventricular involvement is also a risk factor.

Symptomatic ventricular arrhythmias are treated initially with β-blocker therapy, and if β-blockers cannot control a patient’s symptoms or prevent recurrent VT, membrane-active antiarrhythmic agents such as sotalol and, if necessary, amiodarone may be considered. Catheter ablation can be employed to palliate patients with refractory arrhythmias, and cardiac transplantation is considered in patients with progressive heart failure and/or intractable recurrent ventricular arrhythmias. Triggers of sudden cardiac arrest in ARVC include vigorous physical activity, which increases the risk of sudden death in the young fivefold. Accordingly, avoidance of competitive athletics and strenuous exercise is often recommended.

Genetics

ARVC is an autosomal-dominant genetic disorder. If a parent has a disease-causing mutation, the risk to each child of inheriting the mutation is 50%.
Not all mutation carriers are symptomatic. Mutations in at least seven genes together account for ARVC in 40%–50% patients. Five genes that code for desmosome proteins—plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP2), desmoglein-2 (DSG2), and desmocollin-2 (DSC2)—as well as two other nondesmosomal genes (RYR2 and TMEM43) have been associated with ARVC (Table 2).

**TABLE 2: Genes associated with ARVC**

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>GENE NAME</th>
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<tr>
<td>DSC2</td>
<td>Desmocollin 2</td>
</tr>
<tr>
<td>DSP</td>
<td>Desmoplakin</td>
</tr>
<tr>
<td>DSG2</td>
<td>Desmoglein 2</td>
</tr>
<tr>
<td>PKP2</td>
<td>Plakophilin 2</td>
</tr>
<tr>
<td>RYR2</td>
<td>Ryanodine receptor 2</td>
</tr>
<tr>
<td>JUP</td>
<td>Plakoglobin</td>
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<tr>
<td>TMEM43</td>
<td>Transmembrane protein 43</td>
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**Indications and Utility of Genetic Testing**

Genetic testing for ARVC involves screening for all seven genes in table 2. Diagnostic genetic testing can be considered for symptomatic patients with ARVC, and predictive testing considered for asymptomatic patients with a known familial mutation or positive family history of ARVC. Testing should initially be performed on a symptomatic family member with ARVC. Preferably, the most severely affected family member should be tested first. In some cases, genetic testing can be performed on a deceased individual if the medical examiner has stored blood or tissue that can be used for genetic testing. Testing a symptomatic family member is done to attempt to identify the familial mutation.

Genetic testing in a clinically affected patient with ARVC may be used to confirm the diagnosis of ARVC and assist in the medical management of family members. Identification of a mutation in the family can lead to genetic identification of at-risk family members who are clinically asymptomatic and who may have normal ECGs and echocardiograms. Family members who test positive for the familial mutation should have regular cardiac evaluations. Alternatively, a negative genetic test result for the familial mutation would obviate the need for repeated follow-up examinations. Genetic testing may also be used for prenatal or preimplantation genetic diagnosis.
Genetic Testing Results and What They Mean

The three possible outcomes of genetic testing are positive, negative, and variant of unknown clinical significance (VOUS). All patients who undergo genetic testing should receive pre-test and post-test genetic counseling so they can understand the implications of testing. Genetic counseling services can be found at www.nsgc.org.

- **Positive result:**
  A positive test result indicates that a disease-causing mutation was identified in that individual. This finding confirms the diagnosis of ARVC and provides valuable information to family members. All first-degree relatives (children, siblings, parents) of the proband may then be offered predictive genetic testing to identify their risk for ARVC. If a family member is found to be positive for the familial mutation, this individual is considered to be at risk for ARVC. It is important to note that there is phenotypic variability even within family members who have been identified with the same mutation.

- **Negative result:**
  A negative result in an affected individual does not rule out ARVC, and the patient should be managed according to his/her clinical symptoms. Possible reasons for a negative result could be that (1) the patient may have a mutation in a gene not evaluated by the testing panel, (2) the patient may have a mutation in a part of an ARVC gene that was not covered in the test, or (3) the patient has a cardiac condition other than ARVC. Predictive genetic testing of family members when the affected family member testing is negative is neither informative nor warranted. Family members of a clinically affected individual with negative test results may still be at risk for ARVC and thus should be regularly screened by a cardiologist.

If an asymptomatic individual is negative for a mutation identified in a family member, this person is considered a true negative and is not at increased genetic risk for familial ARVC. Clinical monitoring for this individual is not necessary, but this patient could, of course, develop other types of cardiac disease in the future.

If there are no symptomatic members of an ARVC family available for testing, an asymptomatic individual may pursue predictive genetic testing prior to identification of the familial mutation. However, if the asymptomatic family member is found to have a negative test result, this result is considered an uninformative negative, and this asymptomatic family member should still be followed by serial examinations that could include EKG, echocardiogram, and Holter monitoring, as the genetic test identifies mutations in only 40%–50% of families with ARVC.
• **Variant of unknown clinical significance (VOUS):**
  A VOUS result indicates that the pathogenetic role of the observed DNA variant cannot be clearly established. Before declaring a gene variant to be a VOUS, it has to be tested in a large series of normal individuals (controls) and not observed in the panel of controls. To further clarify the clinical significance of a VOUS, testing of family members is often helpful. If an affected adult relative is found to have the same variant as the patient, it is more likely that the variant is disease causing. The greater the number of affected family members who carry the VOUS, the greater the likelihood that the VOUS is pathogenic. If it is found that there is consistent linkage of the VOUS with symptoms of ARVC in family members, the variant can then be reclassified as a family-specific mutation, and extended family members can be offered predictive genetic testing.

**References**


2. Thiene G, Corrado D, and Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007: 2(45); 1-16.


About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients and clinicians in diagnosing rare inherited disorders. Currently, GeneDx offers testing for more than 300 rare Mendelian disorders, oligonucleotide-microarray-based testing for detection of chromosomal abnormalities, testing for autism spectrum disorders, and gene panels for testing various forms of inherited cardiac disorders. Our highly trained and experienced physicians, geneticists, and genetic counselors work as a team to bring gene discoveries to clinical medicine for use in direct patient care. We invite you to visit our website, www.genedx.com, to learn more about us and the services we offer.