Arrhythmogenic right ventricular dysplasia: from genetics to treatment

Aritimojenik sağ ventriküler displazi: Genetikten tedaviye

Aslam Khan, Suneet Mittal, Mark V. Sherrid

Division of Cardiology, St. Luke’s-Roosevelt Hospital Center, Columbia University College of Physicians & Surgeons, New York, NY, USA

ABSTRACT

Arrhythmogenic right ventricular dysplasia (ARVD), also known as arrhythmogenic right ventricular cardiomyopathy, is a genetic cause for sudden cardiac arrest. In ARVD, there is progressive replacement of normal myocytes, with fat and fibrous tissue, predominantly in the right ventricle that predisposes the individual to arrhythmias. Patients who are identified with this condition are risk stratified; those at high risk are recommended to have implanted cardioverter defibrillators. (Anadolu Kardiyol Derg 2009; 9: Suppl 2; 24-31)

Key words: Arrhythmogenic right ventricular dysplasia, implantable cardioverter defibrillator, sudden cardiac death

ÖZET


Anahtar kelimeler: Aritmojenik sağ ventriküler displazi, takılabilen kardiyoverter defibrilatör, ani kardiyak ölüm

Epidemiology

Arrhythmogenic right ventricular dysplasia (ARVD) has been reported to affect anywhere from 1 in 1000 to 1 in 5000 individuals (1, 2). This variability may stem from observations that the diagnosis is difficult to make, and it can be mistaken for other disease states. Also, importantly, ARVD has a higher prevalence in certain communities, the best well known in northeast Italy. Clinically, ARVD is an important cause of sudden death in individuals <30 years of age and has been found in up to 22-23% of sudden deaths in young people in some locales (3, 4).

Genetics

Thirty to 50% cases of ARVD occur in families (5-8). This may be an underestimation, as the genes responsible for this disease may have low penetrance and there may be variable expression. Low penetrance and variable expression make it difficult to trace the disease along a family line.

The genes responsible for ARVD follow two forms of inheritance, autosomal dominant and autosomal recessive. The autosomal dominant form is the most common. The autosomal recessive form is mainly associated with a certain syndromes with simultaneous cardiac and cutaneous involvement. The most well recognized autosomal recessive form of ARVD is called Naxos disease (named for the Greek island where it was first noted), in which there is ARVD along with disorders of the skin and hair (9). Other conditions similar to Naxos disease have also been linked to an autosomal recessive inheritance of mutant genes (10, 11).

Depending on the loci of the affected gene or mutation, twelve different genetic variants of ARVD have been described (ARVD 1-ARVD12) (Table 1). An overwhelming majority of these mutations code for proteins responsible for maintaining the structural integrity of the heart, the desmosomes. Desmosomes are complex multiprotein structures of the cell membrane that provide structural and functional integrity to adjacent cells (Fig. 1). They are found in tissues that experience mechanical stress, including...
epidermis and myocardium. At least three groups of protein families contribute to the formation of desmosomes: plakins (desmoplakin and desmin), Armadillo-repeat proteins (plakoglobin and plakophilins), and desmosomal cadherins (desmocollins and desmogleins). Desmin proteins are a part of the cytoskeleton and attach the cytoskeleton to desmoplakin. ARVD 7 is associated with mutation in the gene coding for desmin. Desmoplakin gene mutation was the first mutation identified with autosomal dominant ARVD and is associated with ARVD 8 (12). The desmoplakin protein connects desmin to the Armadillo repeat proteins, plakoglobin and plakophilin-2. The Armadillo repeat proteins, associated with ARVD 9 and 10, connect desmoplakin, and in turn desmin and the cytoskeleton to the desmosomal cadherins, desmocollin and desmoglein (13, 14). ARVD 11 and 12 affects desmoglein-2 and desmocollin, respectively (15, 16). These cadherins extend through the cytoplasmic membrane and serve as transmembrane adhesion molecules attaching to their counterparts on adjacent cells.

In addition to mutations in genes coding for proteins associated with desmosomes, other genes coding for proteins not associated with desmosomes have been identified. ARVD 1 is associated with a mutation in TGF-beta-3 gene (17). This mutation results in overexpression in TGF-beta-3 and may result in myocardial fibrosis. Mutations in RyR2 (usually associated with catecholaminergic polymorphic ventricular tachycardia) is associated with ARVD 2 (18). ARVD 5 is associated TMEM-43 gene (19). Mutation of this gene causes dysregulation of adipogenic pathway regulated by PPAR gamma and may explain fibrofatty infiltration of the myocardium in this form of ARVD.

In patients affected with ARVD, comprehensive screening for gene mutations will yield a positive result in approximately 40 to 50% of cases (20). Sequence analysis is the mainstay of genotyping in ARVD because of marked allelic heterogeneity, and frequent “private” mutations (20). Genetic counseling for families of patients who have a relative with ARVD should be included in routine care, including sequence analysis, when possible. Genotyping has two roles: first, it will allow confirmation of ARVD in index cases and, second, it will allow for efficient cascade screening of extended family members. Armed with knowledge of the specific mutation in the proband, clinicians can employ focused specific genetic analysis to screen family members. Due to the slowly progressive nature of this disease, asymptomatic family members found to have genes linked to ARVD should be monitored aggressively for development of this disease. However, the role of genotyping for prognosis is not well defined, and currently genotyping should not be used for risk stratification.

Table 1. Genetic Abnormalities Associated with ARVD

<table>
<thead>
<tr>
<th>ARVD Type</th>
<th>Protein / Chromosome</th>
<th>Mutation Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVD 1</td>
<td>TGF-beta-3</td>
<td>Myocardial Fibrosis</td>
</tr>
<tr>
<td>ARVD 2</td>
<td>RyR2</td>
<td>Impaired Calcium Handling</td>
</tr>
<tr>
<td>ARVD 3</td>
<td>11q42-q43</td>
<td>--</td>
</tr>
<tr>
<td>ARVD 4</td>
<td>2q32.1-q32.3</td>
<td>--</td>
</tr>
<tr>
<td>ARVD 5</td>
<td>TMEM-43 gene</td>
<td>Fibrofatty infiltration</td>
</tr>
<tr>
<td>ARVD 6</td>
<td>10p12-14</td>
<td>--</td>
</tr>
<tr>
<td>ARVD 7</td>
<td>Desmin</td>
<td>Impaired Desmosomal Function</td>
</tr>
<tr>
<td>ARVD 8</td>
<td>Desmoplakin</td>
<td>Impaired Desmosomal Function</td>
</tr>
<tr>
<td>ARVD 9</td>
<td>Plakoglobin</td>
<td>Impaired Desmosomal Function</td>
</tr>
<tr>
<td>ARVD 10</td>
<td>Plakophilin-2</td>
<td>Impaired Desmosomal Function</td>
</tr>
<tr>
<td>ARVD 11</td>
<td>Desmoglein-2</td>
<td>Impaired Desmosomal Function</td>
</tr>
<tr>
<td>ARVD 12</td>
<td>Desmocollin</td>
<td>Impaired Desmosomal Function</td>
</tr>
</tbody>
</table>

ARVD-arrhythogenic right ventricular dysplasia

Figure 1. Simplified schematic of desmosomal structure

(Reproduced from reference 23 with permission from Blackwell Futura Publishing, Inc., Copyright 2005)
Furthermore, the current limitation to the widespread implantation of genotyping remains cost, though with competition between vendors, costs are decreasing rapidly in the U.S.

**Pathophysiology**

Regardless of the mode of inheritance, it appears that the majority of mutant ARVD genes code for proteins that make up desmosomes, which are intracellular adhesion complexes that provide mechanical connections between cardiac myocytes. When placed under mechanical stress, the impaired desmosomes cause myocytes to detach from each other leading to cell death (22, 23). This cell death causes inflammation with scar formation and fat deposition.

Fatty replacement involves the whole thickness of the right ventricle (RV) in 45% of cases, the outer half of RV free wall in 27%, and the outer two-thirds in 28% of cases. These fibrofatty islands act as areas of reentry giving rise to ventricular tachycardia (VT). Initially the disease process is localized, occurring in three discrete areas of the RV known as the “triangle of dysplasia” (24). This triangle describes the areas involved: the posterior wall, the apex, and the outflow tract of the RV. Gradually the disease spreads from these discrete areas to involve the rest of the RV. The left ventricle (LV) and the interventricular septum are usually spared. If LV involvement occurs, it tends to occur as a late manifestation.

**Clinical Presentation**

When symptoms are present, they tend to occur around 30 yrs of age. However, patients’ age can range from 10 to 50 years (4, 25). Men and women are equally affected. The most common symptoms of ARVD are due to arrhythmia. Symptoms include palpitations, dizziness, shortness of breath, syncope, or near syncope. Unfortunately, sudden cardiac arrest (SCA) may also be the presenting symptom; patients with no prior symptoms may present with SCA (8, 26). Some patients may be asymptomatic, and the diagnosis of ARVD is suspected due to a positive family history or findings on noninvasive tests such as an echocardiogram or electrocardiogram (ECG) (27).

As previously mentioned, the replacement of normal heart muscles with fat and fibrous tissue predispose to the development of arrhythmias. The most common type of arrhythmia initiates from the RV, as this is the site with the largest amount of fibrofatty infiltration. The arrhythmias may range from premature ventricle contractions to sustained VT. On a surface ECG, this VT has a left bundle branch block morphology, indicating RV origin.
The VT may have either an inferior or superior axis, depending if the site of origin is near the base or apex of the heart, respectively (Fig. 2). Furthermore, as the VT tends to be reentrant around a fixed scar, it is monomorphic. Often patients may have bursts of nonsustained VT (NSVT) and frequent premature ventricular contractions (VPC). The VPCs and NSVT may have subtle differences in morphologies during subsequent episodes. This helps in differentiate ARVD from other causes of VT of RV origin (Fig. 3). The frequency of such arrhythmias in ARVD varies with the severity of the disease. Patients with severe forms of the disease tend to have arrhythmias more frequently. There seems to be an increased association of VT and SCA with exercise in patients with ARVD (26, 28, 29). It is presumed that genetically predisposed athletes have increased mechanical

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
<td>Family history of premature sudden death (&lt;35 years) caused be suspected ARVD</td>
</tr>
<tr>
<td>ECG depolarization/conduction abnormalities</td>
<td>Epsilon waves or prolongation of the QRS complex (≥ 110 msec) in the right precordial leads (V1 – V3)</td>
<td>Late potentials seen on signal averaged ECG</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>Inverted T waves in the right precordial leads in patients &gt;12 years in the absence of right bundle branch block</td>
<td></td>
</tr>
<tr>
<td>Tissue characterization of walls</td>
<td>Fibrofatty replacement of myocardium on endomyocardial biopsy.</td>
<td>Mild global RV dilation or ejection fraction reduction with normal LV</td>
</tr>
<tr>
<td>Global or regional dysfunction and structural alterations</td>
<td>Severe dilation and reduction of RV ejection fraction with minimal LV involvement</td>
<td></td>
</tr>
<tr>
<td>Localized RV aneurysms</td>
<td>Mild segmental dilation of the RV</td>
<td>Regional RV hypokinesia</td>
</tr>
<tr>
<td>Severe segmental dilation of the RV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Criteria for diagnosis of arrhythmogenic right ventricular dysplasia (Adapted from reference 32)

Figure 4. Electrocardiogram in a patient with ARVD

ARVD - arrhythmogenic right ventricular dysplasia, ECG - electrocardiogram, LV - left ventricle, RV - right ventricle
stress placed on the heart, resulting in increased desmosomal disruption and promoting a more severe and advanced form of the disease. Also exercise leads to increased catecholamine levels that may predispose to development of VT. Anyone identified with ARVD should avoid competitive athletics or extremes of physical exertion because these activities would predispose to SCA (30).

**Diagnosis**

The diagnosis of ARVD presents a difficult challenge. Even normal hearts have some degree of fat and fibrous tissue. Generally, there is an effort to document abnormal areas of right ventricular dilatation and function with echocardiography and magnetic resonance imaging (MRI). However, echocardiography and MRI may be inaccurate at detecting abnormal motion of the RV. Also, the ECG abnormalities seen in ARVD can occur in different disease states and thus patients may be mislabeled as having ARVD. Conversely, requiring just one specific finding might lead to a missed diagnosis in a patient who truly has ARVD (31).

ARVD should be considered in patients who present with VT arising from the RV (Fig. 2, 3) in the absence of overt heart disease, or in cases of SCA, occurring particularly during exercise. In order to improve the accuracy of diagnosis, a list of diagnostic criteria has been formulated (Table 2) (32). These criteria consist of findings typically seen in ARVD and cover several different diagnostic modalities. They include the patient’s family history, patient’s own history of arrhythmias, ECG findings (Fig. 4), findings on imaging studies and on biopsy. Among these broad categories, the criteria are divided into major and minor. A diagnosis of ARVD can be made when two major criteria, or one major plus two minor criteria, or four minor criteria alone are met. This combination of criteria helps detect patients who truly have the disease. Even with these criteria, patients with less severe forms of the disease can be missed.

**Electrocardiographic Features**

Patients suffering from ARVD often have or will develop an abnormal ECG in during sinus rhythm (33). Common findings include inverted T waves in the right precordial leads (V1-V3). This finding may be seen in <3 % of healthy subjects but is seen in 87% of patients with ARVD (34). The T wave inversions indicate abnormal repolarization of the right ventricle and become more prominent as the disease advances. Persistent T wave inversions in the right precordial leads after the age of 12 is a minor criteria for the diagnosis of ARVD. Secondly, a suggestive finding for ARVD in the right precordial leads is the presence of an epsilon wave (Fig. 4). This seen as a low amplitude signal at the junction of the QRS complex and the ST segment. Sensitivity for epsilon waves ranges from 9 -33% (35, 36). Twenty six percent of patients with ARVD will have an incomplete right bundle branch block pattern with a QRS duration >110 msec in the right precordial leads (35). The presence of either a prolonged QRS duration or epsilon waves are a major criterion for the diagnosis of ARVD. Prolonged S-wave upstroke ≥55 ms in leads

**Table 3. High risk features in patients with arrhythmogenic right ventricular dysplasia. Patients in whom ICD implantation for the prevention of SCA may be considered**

- Patients who present with unexplained syncope
- Patients with history of cardiac arrest or sustained VT
- Patients with clinical signs of RV failure
- Patients with LV involvement
- Family history of SCA
- Patients with Naxos disease

ICD - implantable cardioverter defibrillator, LV - left ventricle, RV - right ventricle, SCA - sudden cardiac arrest, VT - ventricular tachycardia
V1 to V3 may be seen in up to 24% of patients with ARVD. All these findings indicate slowed conduction in the RV, which in the setting of ARVD are secondary to fibrofatty infiltration. Since none of the above findings is specific for ARVD, it is important to view the ECG in the clinical context.

Signal averaging of ECG allows for detection of late and low amplitude potentials, which may be difficult to detect on a standard surface ECG, and serves as a minor criteria for the diagnosis ARVD (Fig. 5). A signal averaged electrocardiogram (SAECG) is considered abnormal when two out of the three following findings are present: 1) a filtered QRS duration ≥114 milliseconds, 2) the presence of low amplitude signals of less than 40 microvolt that persist >38 milliseconds in the terminal portion of the filtered QRS, and 3) a root mean square voltage of <20 microvolt of signal in the last 40 milliseconds of the filtered QRS complex. Similar to the abnormalities seen on a surface ECG an abnormal SAECG is indicative of slowed conduction in diseased myocardium. However, these findings are not specific for ARVD and may be seen in other cardiomyopathies.

**Imaging of the Right Ventricle**

Several modalities exist for imaging of the RV including right ventricular cineangiography, echocardiography, and cardiac MRI (32). No one imaging technique is considered a gold standard and all require additional evidence to make a diagnosis of ARVD. Initially, ventricular cineangiography was widely used to assess RV function. However, because it is invasive, subject to interobserver variability, and has a decreased sensitivity for mild disease, it is less commonly employed. Echocardiography provides a readily available noninvasive approach to evaluation of right ventricular function and is often used as the initial imaging test in index cases of ARVD and screening of family members (37-39). A limitation of echocardiography may be insensitivity to subtle RV dysfunction in the early stages of the disease. Cardiac MRI has emerged as an excellent tool for imaging the RV (40-42). Using black blood images and delayed enhancement with gadolinium, MRI allows for the detection of areas of fat and fibrosis in addition to evaluating RV function (Fig. 6). A limitation with MRI remains availability and experience. Often normal hearts will have subtle abnormalities and areas of fat, which may be misinterpreted as being consistent with ARVD. Regardless of the imaging modality used, presence of segmental RV dilation, aneurysmal areas in the RV, and RV hypokinesia in concert with normal LV function helps support the diagnosis of ARVD.

**Myocardial Biopsy**

Since ARVD involves focal areas of the RV and spares the interventricular septum, myocardial biopsy tends to have a low sensitivity and specificity. Myocardial biopsy of the right ventricular free wall may increase the diagnostic yield, at the risk of increased perforation. Moreover, some degree of fat is interspersed between myocytes in healthy individuals, affecting the specificity of the biopsy sample. Conversely, in early stages of ARVD changes to the myocardium may not be well developed and not detected. Using variable diagnostic cut-offs for healthy tissue, fat and fibrosis and obtaining samples from the triangle of dysplasia may increase the diagnostic accuracy of myocardial biopsy (43). Furthermore, myocardial biopsy is helpful in differentiating other diseases that may mimic ARVD such as sarcoidosis (44).

### Table 4. Proposed modification of task force criteria for the diagnosis of familial arrhythmogenic right ventricular dysplasia. Proposed criteria used for periodic screening of relatives of patients with arrhythmogenic right ventricular dysplasia in order to assess for development of the disease.

<table>
<thead>
<tr>
<th>ARVD in First-Degree Relative Plus One of the Following:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ECG</td>
<td>T-wave inversion in right precordial leads (V₂ and V₃)</td>
</tr>
<tr>
<td>2. SAECG</td>
<td>Late potentials seen on signal-averaged ECG</td>
</tr>
<tr>
<td>3. Arrhythmia</td>
<td>LBBB type VT on ECG, Holter monitoring or during exercise testing</td>
</tr>
<tr>
<td>4. Structural or functional abnormality of the RV</td>
<td>Mild global RV dilatation and/or EF reduction with normal LV</td>
</tr>
<tr>
<td></td>
<td>Mild segmental dilatation of the RV</td>
</tr>
<tr>
<td></td>
<td>Regional RV hypokinesia</td>
</tr>
</tbody>
</table>

ARVD - arrhythmogenic right ventricular dysplasia, ECG - electrocardiogram, EF - ejection fraction, LBBB - left bundle branch block, RV - right ventricle, SAECG - signal-averaged electrocardiography, VT - ventricular tachycardia

*Previously >1,000/24-h period in task force criteria

(29) *Previously >1,000/24-h period in task force criteria

Recently, Asimaki and colleagues (45) used routine immunohistochemical analysis of a conventional myocardial biopsy sample to develop a highly sensitive and specific test for ARVD. While results of this study need to be validated, a marked reduction in immunoreactive signal levels for plakoglobin with normal signal levels for the nondesmosomal adhesion molecule N-cadherin diagnosed ARVD in myocardial biopsy samples with a sensitivity of 91%, a specificity of 82%, a positive predictive value of 83%, and a negative predictive value of 90%. These findings were seen independent of site of biopsy and the presence of desmosomal gene mutation.

### Differential Diagnosis

Several conditions may give rise to VT originating from the RV: these include ischemic and nonischemic dilated cardiomyopathies, cardiac sarcoidosis, congenital heart disease, and idiopathic RV outflow tract tachycardias. The diagnosis of ARVD is more likely in patients with isolated RV dysfunction with normal LV function and pulmonary artery pressures. Secondary causes for RV dysfunction such as pulmonary regurgitation or stenosis must be excluded. In one report, the incidence of cardiac sarcoidosis was as high as 15%. Left ventricular dysfunction and histological findings help discriminate between the two entities (44). Uhl’s disease is a rare congenital disease in which there are areas of complete absence of myocardium in the RV. These patients usually present in infancy with symptoms of heart failure and ventricular arrhythmias are rare (46). Idiopathic VT involving the right ventricular outflow tract may be indistinguishable from early stages of ARVD. Both groups of patients tend to be young, have normal LV function - and have VT with a left bundle branch morphology and an inferior axis, which is associated with exercise. Distinguishing the two entities is of critical importance as patients with idiopathic VT have excellent outcomes and can be cured with radiofrequency ablation while patients with ARVD...
may experience sudden death. Idiopathic VT patients usually have normal LV and RV function on imaging, lack any family history, and have normal ECG and SAECG findings. PVCs and VT in idiopathic VT are of uniform morphology. Their tachycardia can be terminated with vagal maneuvers and the administration of adenosine because it is secondary to triggered activity. In contrast, VT in ARVD may contain several morphologies of VT and PVCs due to varying pathways of reentry. The mechanism for the arrhythmia is reentry, and it thus is not responsive to adenosine, a distinguishing characteristic (Fig. 3).

**Treatment**

Currently, there is no curative treatment. The goal of therapy is to prevent death from VT and SCA. This is effectively accomplished by using implanted cardioverter-defibrillator (ICD). ICD implantation is generally recommended for patients who have had a documented episode of sustained VT or SCA (21). Patients who have certain high-risk features for SCA (Table 3) but who have not had an episode of VT or SCA, an ICD for primary prevention may be considered (21, 47). Care must be utilized in the appropriate allocation of ICD to those at highest risk of SCA. The benefit of implanting ICDs in low risk patients, where the risk of SCA may accumulate over time, must be outweighed by the risk of the ICD complications, which also increase with time (48). This is particularly an issue in the young.

Use of antiarrhythmic drugs (AADs), i.e. sotalol, is reserved for patients who are not candidates for ICD or after ICD implantation to prevent frequent ICD discharges (21, 49). Limited data exists for the use of AADs in patients with ARVD. In one study of 84 patients, the class III AAD, sotalol, had an efficacy rate of 68% in the EP lab in patients initially inducible with VT during electrophysiological testing. In patients in whom VT became not inducible during electrophysiologic testing after sotalol, 83% had no VT at 34 months. These rates are much higher compared to efficacy rates for class I AAD (0-17%) and amiodarone (15-25%) (50). Currently when the use of AADs is needed in patients with ARVD, sotalol or amiodarone are the AADs of choice. It is important to note that no AAD has proven to reduce the risk of SCA and a survival benefit is only expected with ICD implantation.

Radiofrequency ablation (RFA) targeted to the site of the arrhythmia may be occasionally be recommended for high risk patients who are not candidates for an ICD, or those who have arrhythmias refractory to treatment, post ICD (21). In this context, indications for RFA are similar to those of AAD. As mentioned previously, increased physical activity may advance disease and lead to arrhythmias. Thus, patients with ARVD should not participate in competitive sports or in activities in which loss of consciousness may lead to harm e.g. scuba diving. Low intensity activities such as golf are considered safe (30).

**Prognosis**

The overall prognosis in ARVD is not clear. Small retrospective analysis of patients with ARVD has quantified an annual mortality of 2.3%. As may be expected, patients with mild disease and non-sustained episodes of VT tend to have a relatively better prognosis than patients with severe disease, a history of sustained VT, or evidence of right or left sided heart failure.

**Family Screening**

Family members of affected patients should be screened to see if they have inherited ARVD. This may be done be either by 1) gene guided strategy described above, or by 2) periodically non-invasively testing family members using modified diagnostic criteria, which takes into account minor abnormalities of the ECG, Holter, or echocardiographic criteria (Table 4). Periodic testing is advised with the non-invasive testing route, as with time, relatives may develop ARVD.

**Conclusion**

Our understanding of ARVD has increased tremendously in a few short years. It is important to identify patients who suffer from this condition and risk stratify them appropriately. Patients at high risk are implanted with ICDs. Currently, antiarrhythmic drugs and radiofrequency ablation should be reserved as adjunctive therapy to ICD in those with uncontrollable VT, or as primary therapy in those who ICD implantation is contraindicated.

**References**


