Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Yongkeun Cho, MD
Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea

ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is characterized by progressive, fibrofatty replacement of the myocardium, ventricular arrhythmia, sudden death, and progressive heart failure. ARVC/D may be an important cause of syncope, ventricular arrhythmias, electrocardiogram (ECG) abnormalities and/or non-ischemic wall motion abnormalities. Some patients, however, do not have a typical clinical presentation. Thus, a high clinical suspicion and extensive studies may be needed to establish the diagnosis of ARVC/D. Recent progress in diagnostic modalities and a better understanding of the clinical manifestations of ARVC/D may lead to optimal management of affected patients. (Korean Circ J 2008;38:514-523)

KEY WORDS: Cardiomyopathies; Arrhythmia; Right ventricle.

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a primary disease of heart muscle characterized by progressive, fibrofatty replacement of the right ventricle (RV) and life-threatening ventricular arrhythmias with left bundle branch block (LBBB) morphology.1-8 Twenty-six years have elapsed from the time that the clinical profile of ARVC/D was first described.1 ARVC/D in animals, such as cats and dogs, have also been reported.9,10

The estimated prevalence of ARVC/D in the general population ranges from 1 in 2,000 to 1 in 5,000.11 This 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.’

Etiology

Several reports have suggested a familial pattern for ARVC/D;11,12,13 however, the precise etiology of ARVC/D remains to be established. ARVC/D is typically inherited as an autosomal dominant trait with incomplete penetrance and variable expression,12,13 implicating environmental factors and other genetic modifiers in the etiology of this disease. An autosomal recessive form associated with palmoplantar keratosis is called Naxos disease. The locus for Naxos disease has been located on chromosome 17q21.14 A mutated gene produces a protein called plakoglobin is involved in the genesis of the disease.15 A recessive mutation in the desmoplakin gene has also been described as the etiology of Naxos disease.16 Disease loci for the autosomal dominant form of ARVC/D have been mapped to chromosomes 14q23-24, 1q42-q43, 14q12-q22, 2q32, 3q23, 10p12-p14, 10q22, and 6p24.17-22 Apoptosis has also been proposed as the underlying mechanism in the pathogenesis of this disease.23,24

Incidence and Prevalence

The incidence is unknown since this pathologic process can be completely asymptomatic in the young, with sudden death as the initial manifestation.7,13,25 However, a prevalence of approximately 1 in 5,000 people has been estimated.11 ARVC/D has been found in up to 20% of sudden deaths in young people and it is considered the most common cause of exercise-related sudden death among young Italian athletes.25 The incidence of a familial pattern varies from 15-50% with the study population and method.12,13,16,27

Natural History

Classically, the natural history of ARVC/D is considered to include four distinct phases. In the first phase, the concealed phase, patients are often asymptomatic,
but may nevertheless be at risk for sudden death, especially during exertion. Structural changes are subtle and may be confined to one region of the so-called “triangle of dysplasia” (the inflow, outflow, and apical portions of the RV). Symptomatic ventricular arrhythmia is seen in the second phase, the overt electrical disorder phase, accompanied by more obvious morphologic and functional abnormalities of the RV. The third phase is the RV failure phase characterized by diffuse RV disease, which results in right-sided heart failure with relatively preserved left ventricular (LV) function. Notable LV involvement with biventricular pump failure occurs in the fourth biventricular pump failure stage, leading to a phenotype that may resemble dilated cardiomyopathy. A multicenter study of patients with a pathologic diagnosis of ARVC/D at transplantation or autopsy found evidence of fibrofatty replacement of the LV in more than two-thirds of the hearts examined. LV involvement correlated with age, arrhythmic events, and clinical heart failure.

Another recent European study described the annual mortality rate of 2.3%. Progressive heart failure was the cause of death in more than one-half of patients, whereas sudden death occurred in less than one-third of patients. In this series, the high prevalence of death due to heart failure may be explained by a change in the cause of death from sudden death to non-sudden death due to aggressive therapeutic management, including ablation, implantable cardioverter-defibrillator (ICD), and surgical treatment. In another study of family members, the yearly mortality rate was very low (0.08 patient per year).

These data illustrate the wide spectrum of the natural history of the disease, and the presence of subgroups of patients with variable degrees of risk.

Pathology

Dilatation of the RV, aneurysmal dilatations of the infundibular, apical and subtricuspid areas, and replacement of normal myocardium with fibrofatty tissue and thinning of the RV wall are commonly observed in cardiac tissues obtained from patients with ARVC/D. The interventricular septum and the LV are spared until late stages of the disease. As the pathologic process advances from the epicardium to the endocardium, an endocardial biopsy obtained from a suspected case may be normal. Two types of ARVC/D, fatty and fibrofatty types, were proposed 30 years ago. However, pure fatty infiltration of the RV, per se, is a different process that may not be considered synonymous with ARVC/D. The diagnosis of ARVC/D should be made in the presence of fibrosis, which is more arrhythmogenic than pure fatty infiltration. The other histologic finding which exists in patients with ARVC/D is lymphocytic infiltration of the myocardium. Younger patients dying with fibrofatty ARVC/D may have a more lethal or aggressive form of the disease, characterized by myocardial inflammation. Another controversy which persists regarding ARVC/D is the clinical significance of conduction abnormalities, as reported in a French study.

Symptoms

The clinical presentation varies from silent forms with an exercise-related episode of syncope or sudden death as the initial manifestation, to biventricular failure that requires cardiac transplantation. RV failure is usually observed in older patients. Common symptoms include palpitations, fatigue, dizziness, atypical chest pain, and syncope. The mechanism of sudden death in ARVC/D is known to be an acceleration of ventricular tachycardia (VT) with ultimate degeneration into ventricular fibrillation (VF). ARVC/D should be suspected in all young patients presenting with syncope, VT, or cardiac arrest. Patients with ARVC/D most commonly come to clinical attention because of ventricular arrhythmias. The ventricular arrhythmias that originate in the diseased RV may be asymptomatic and detected by routine ECG, or they may cause symptoms, such as palpitations, syncope, or sudden cardiac death. Exercise has been identified as a common precipitant of arrhythmias that occur in ARVC/D.

Physical Examination

About one-half of patients have normal findings on physical examination. With severe RV dilation, tricuspid regurgitation murmur and giant a waves may be observed.

Diagnosis

In 1994, the Task Force of the Working Group on Cardiomyopathies proposed diagnostic criteria for ARVC/D (Table 1). This task force was established because the diagnosis of ARVC/D may be difficult due to several problems, such as non-specific ECG abnormalities, the diverse potential etiologies of ventricular arrhythmias with a LBBB morphology, the technical difficulties in assessing RV structure and function, and the interpretation of the endomyocardial biopsy findings. The diagnosis of ARVC/D is fulfilled when two major criteria or one major criterion plus two minor criteria or four minor criteria exist from different groups. The criteria are highly specific, but lack sensitivity. Diagnosis at an early stage remains a clinical challenge. The aetial evaluation of patients with suspected ARVC/D is recommended as clinical features may develop during the
It has been recommended that patients suspected to have ARVC/D undergo a thorough initial evaluation with non-invasive testing. Standard non-invasive testing for ARVC/D includes a 12-lead ECG, echocardiography, signal-averaged ECG, Holter monitoring, and cardiac magnetic resonance imaging. If non-invasive testing reveals findings consistent with ARVC/D, then invasive testing, including RV angiography and a RV endomyocardial biopsy, are recommended to confirm the diagnosis.

A definite diagnosis of ARVC/D is based on histologic demonstration of transmural fibrofatty replacement of the RV myocardium obtained at autopsy or surgery. Myocardial biopsy lacks sufficient sensitivity to establish the diagnosis because the biopsy is performed mostly in the interventricular septum, whereas the typical pathologic changes of ARVC/D are more pronounced in the RV free wall. It is important not to rely on any single criteria to arrive at a diagnosis of ARVC/D, particularly imaging studies. All reasonable efforts should be made to firmly establish the diagnosis.

Routine ECG

ECG abnormalities are detected in most patients with ARVC/D (Table 2). T-wave inversion beyond V; in a young- or middle-aged patient with no apparent

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### Table 1. Task Force of the Working Group on Cardiomyopathies diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>I Global and/or regional dysfunction and structural alterations</td>
<td>Severe dilation and reduction of right ventricular ejection fraction with no (or only mild) left ventricular impairment</td>
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<tr>
<td></td>
<td>Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)</td>
</tr>
<tr>
<td>II Tissue characterization of walls</td>
<td>Severe segmental dilation of the right ventricle</td>
</tr>
<tr>
<td>III Repolarization abnormalities</td>
<td>Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
</tr>
<tr>
<td>IV Depolarization/Conduction abnormalities</td>
<td>Epsilon waves or localized prolongation (&gt;110 ms) of the QRS complex in right precordial leads (V; V;)</td>
</tr>
<tr>
<td>V Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>VI Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
</tr>
</tbody>
</table>

To fulfill the appropriate criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy, patients must meet either two major criteria, one major plus two minor criteria, or four minor criteria.

### Table 2. Common ECG features in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia

<table>
<thead>
<tr>
<th>Electrocardiographic pattern</th>
<th>Reported prevalence in probands (Varies by Cohort)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Up to 40% of patients with symptomatic ventricular tachycardia and right ventricular dysplasia in first year of follow-up</td>
</tr>
<tr>
<td>Depolarization abnormalities</td>
<td></td>
</tr>
<tr>
<td>Complete right bundle branch block</td>
<td>6% to 15%</td>
</tr>
<tr>
<td>Incomplete right bundle branch block</td>
<td>14% to 18%</td>
</tr>
<tr>
<td>Prolongation of QRS complex to &gt;110 ms in V;V; in absence of right bundle branch block</td>
<td>Up to 98% of patients fulfilling task force criteria for right ventricular dysplasia</td>
</tr>
<tr>
<td>Right precordial R-wave reduction</td>
<td>5%</td>
</tr>
<tr>
<td>Epsilon waves in right precordial leads</td>
<td>23% using standard recording technique; 75% when highly amplified and modified recording techniques are employed in adjunct</td>
</tr>
<tr>
<td>Late potentials on signal-averaged ECG</td>
<td>50% to 80%</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td></td>
</tr>
<tr>
<td>Inverted T waves in V;V; in absence of right bundle branch block</td>
<td>54%</td>
</tr>
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</table>

*abnormalities cited in the task force criteria
heart disease, but with ventricular arrhythmias of LBBB morphology, should raise the suspicion of ARVC/D. Another typical ECG feature of ARVC/D is the so-called epsilon waves, which are post-excitation electrical potentials of small amplitude that occur at the end of the QRS complex and at the beginning of the ST segment (Fig. 1). Epsilon waves, which are seen in one-third of patients, are considered a major diagnostic criterion for ARVC/D. Slowed electrical conduction in the RV as a result of ARVC/D may also cause localized widening of QRS complex (≥110 ms) in the right precordial leads, which is seen in two-thirds of the patients. A prolonged S-wave upstroke in V1 through V3 ≥55 ms is the most prevalent ECG feature in most patients and is correlated with disease severity and induction of VT.11)29)38)39) Chest X-Ray

The chest X-ray is usually normal, unless RV enlargement and failure are present.

Signal-Averaged ECG

Late potentials on SAECG recordings are considered a minor criterion for the diagnosis of ARVC/D.15) Usually, when ≥2 of the following criteria are present, late potentials are considered to be present: (1) the duration of the signal-averaged, high-frequency filtered QRS complex ≥114 ms, (2) the duration of the low-amplitude signal of <40 μV in the terminal portion of the filtered QRS complex ≥38 ms, and (3) the root mean square voltage of the terminal 40 ms of the filtered QRS complex <20 μV. An abnormal signal-averaged ECG was present in about two-thirds of the patients,8)29) and some of the family members.26)

Exercise ECG

A symptom-limited exercise stress test is usually performed. Frequent premature ventricular contractions (PVCs), non-sustained VT, and/or sustained VT with exercise were considered abnormal.15)30)

Holter Monitoring

Holter monitoring is considered abnormal when >1,000 PVCs are present in 24 hours.29) The presence of ventricular arrhythmias represents a particularly frequent and characteristic form of presentation.30)33) VF and sudden death can be observed during exercise or physical activity.25)40) However, episodes of sudden death during sleep also occur in patients with normal physical examinations.7)33) Supraventricular arrhythmias, including atrial premature contractions, flutter, tachycardia, and fibrillation have been reported in one-third of patients with ARVC/D and ventricular arrhythmias.40)

Imaging of the RV

RV size and function can be evaluated using a variety of imaging modalities, including 2-D echocardiography, contrast angiography, cardiac magnetic resonance imaging (MRI), and computed tomography (CT). The presence of severe dilatation and/or functional loss of the RV are considered major criterion, and a less severe abnormality in RV size and/or function is considered to be a minor criterion for ARVC/D. However, the definitions of severe and non-severe are unclear and the diagnostic accuracy of each test is uncertain.

RV Contrast Angiography

RV angiography has been regarded as the gold standard for the diagnosis of ARVC/D and has been shown to be highly specific.13) Dyskinetic or akinetic zones in the infundibular, apical, or subtricuspid regions are highly specific findings for ARVC/D; increased end-diastolic volume with abnormal wall motion, persistence
of contrast, multiple outpouchings of the inferior RV wall or aneurysms, tricuspid or mitral valve prolapse, isolated diastolic protrusions, and systolic dyskinesia of the outflow tract are also found. Although the RV volume is nearly always increased, it is often difficult to assess RV enlargement because of the complex geometric shape of the RV.

The invasive nature of the angiographic technique, radiation exposure, and considerable interobserver variability regarding the visual assessment of RV motion abnormalities preclude the use of RV angiography as a primary diagnostic technique for ARVC/D.31

**Echocardiography**

Echocardiography is the most widely used and sensitive technique for assessing cardiac performance in patients with ARVC/D and their family members.8)31)42) The most conspicuous findings on echocardiography are RV dilation, enlargement of the right atrium, isolated dilation of the RV outflow tract, increased reflectivity of the moderator band, localized aneurysms, and decreased fractional area change (Fig. 2).42) RV outflow dilatation is the most common abnormality associated with the task force diagnostic criteria for ARVC/D.42

**Cardiovascular Magnetic Resonance Imaging and Computed Tomography**

One of the most important advances in the diagnosis of ARVC/D has been the introduction of MRI. Noninvasive detection of RV myocardial fibrofatty changes in ARVC/D was made possible by MRI (Fig. 3). MRI findings have an excellent correlation with histopathology and predicted inducible VT, suggesting a possible role in the evaluation and diagnosis of patients with suspected ARVC/D.43

However, limitations of MRI, including interobserver variability, lack of experience at most centers, insufficient resolution for detection of wall thinning, overinterpretation of regional wall motion abnormalities, and difficulties in differentiating normal epicardial fat from true myocardial adipose replacement are known. Thus, the routine use of MRI should not be performed unless an experienced MRI center is available.11) MRI even leads to misdiagnosis of ARVC/D and unnecessary ICD implantation. Diagnosis of ARVC/D cannot rely solely upon quantitative features on MRI.36) Cardiac MR is a valuable component of the diagnostic workup for ARVC/D when performed with a dedicated protocol by experienced specialists.44

CT demonstrates an increase in epicardial adipose tissue delineated by densitometric analysis of the image. This test also shows other morphologic abnormalities described above, such as localized or diffuse compromise, dilatation of the RV, thinning of the wall, hypokinesis, and prominent trabeculations with low attenuation. Multi-detector CT may be an alternative to MRI for patients in whom MRI is a contraindication because of the presence of a pacemaker or ICD.45

**Endomyocardial Biopsy**

Endomyocardial biopsy is recommended for all pa-
Patients suspected of having ARVC/D. It is important to recognize that ARVC/D can be a patchy disease and that clear evidence for the diagnosis will be obtained in approximately one-third of affected individuals. However, when the biopsy shows fibrosis and fatty infiltration, along with surviving strands of myocytes, the diagnosis of ARVC/D is clearly established (Fig. 4). An endomyocardial biopsy is also useful in excluding other conditions, such as sarcoidosis and myocarditis, which can be confused with ARVC/D.11)46)

**Gene Study**

A gene study is not feasible in the majority of cases because of the large genetic heterogeneity and limitation of molecular screening to only a handful of genes that account for minor variants of the disease (Table 3). Therefore, genetic analysis is not currently available for the clinical diagnosis of ARVC/D and is restricted to research laboratories.

Genetic analysis is useful in families with ARVC/D because whenever a pathogenetic mutation is identified, it becomes possible to establish a presymptomatic diagnosis of the disease among family members, to provide them with genetic counseling to monitor the development of the disease, and to assess the risk of transmitting the disease to offspring. On the basis of current knowledge, genetic analysis does not contribute to risk stratification of ARVC/D.47)

**Electrophysiologic Study**

The prognostic role of an electrophysiologic study (EPS) in patients with ARVC/D is controversial. In an Italian study, the limited value of EPS in identifying patients at risk has been demonstrated.49) However, in an...
American study, VT induction was associated with an increased risk for ICD therapy in patients with ARVC/D. Different populations, different types of interventions, different ventricular arrhythmias requiring ICD intervention, and a relatively high rate of ICD therapy in the American trial may explain the differences.

**Differential Diagnosis**

Some patients with localized ARVC/D, particularly in the infundibulum, may exhibit normal RV volumes and a preserved RV ejection fraction, and may present clinically as idiopathic RV outflow tract tachycardia. However, inducibility of VT, presence of more than one ECG morphology, and fragmented potentials may helpful in distinguishing ARVC/D-associated VT from idiopathic RV outflow tract tachycardia. It is important to determine whether the patient has idiopathic VT or ARVC/D for two reasons. First, idiopathic VT is a benign condition and ICD implantation is usually not recommended. Second, because ARVC/D is a hereditary disease, screening all first-degree family members is recommended. Some definite cases of biopsy-proven myocarditis showed typical clinical findings of ARVC/D.

**Risk Stratification**

The available data suggest that young age, prior cardiac arrest, fast and poorly tolerated VT with different morphologies, syncope, severe RV dysfunction, heart failure with LV involvement, and familial occurrence of juvenile sudden death are the major determinants in predicting sudden cardiac death and clinical outcomes with a poor prognosis.

Even the presence of sustained VT in patients with heart failure is an important risk factor. Appropriate ICD therapy during follow-up is also observed frequently in young patients considered to be at high risk with previous cardiac arrest, VT with hemodynamic compromise, and LV involvement.

**Management**

There is no curative treatment for ARVC/D; rather, the aim is to detect patients at high risk and prevent complications. The four therapeutic options for ARVC/D include antiarrhythmic drugs, catheter ablation, ICD implantation, and surgery. Once the diagnosis has been established, treatment should include avoiding competitive sports or vigorous exertion, initiation of a beta-blocker, and consideration for ICD placement. ICDs are recommended for all patients with ARVC/D who have experienced aborted sudden cardiac death or a sustained ventricular arrhythmia. Catheter ablation should be considered in patients with recurrent episodes of VT, despite antiarrhythmic therapy, but should not be considered to be an alternative to ICD therapy. When the disease has progressed to RV or biventricular failure, treatment consists of the current therapy for heart failure, including diuretics, beta-blocking agents, angiotensin-converting enzyme inhibitors, and anticoagulation. In case of intractable RV failure, cardiac transplantation may be the only remaining alternative.

**Antiarrhythmic Agents**

In patients with ARVC/D at low risk for arrhythmic sudden death, specific antiarrhythmic treatment is usually not required. However, should a patient still suffer severe symptoms from palpitations, treatment with conventional antiarrhythmic drugs may be considered. Specific antiarrhythmic drugs or catheter ablation should be limited to patients with significant symptoms refractory to these measures. Sotalol was shown to be the most effective antiarrhythmic drug to prevent inducible VT in patients with ARVC/D in a German study. In the subgroup of high-risk patients, ICD implantation is life-saving and results in improved survival compared with pharmacologic therapy, but antiarrhythmic drugs are often administered to reduce the need for cardioversion or inappropriate interventions.

**Catheter Ablation**

Catheter ablation is considered a palliative procedure in patients suffering from a high frequency of ICD discharges due to recurrent monomorphic VT. Because of the progressive nature of the disease, catheter ablation is not considered to be a curative procedure. Previous studies have shown a favorable acute success rate with catheter ablation of RV tachycardia. However, in patients with ARVC/D, VT recurrences during follow-up are common. The discrepancy between the favorable acute results and the unfavorable long-term outcome may be explained by the progressive nature of ARVC/D, which predisposes to the occurrence of new and malignant arrhythmogenic substrates over time.

**Implantable Cardioverter-Defibrillator**

ICDs are recommended for all patients with ARVC/D who have experienced aborted cardiac death or a sustained ventricular arrhythmia. However, no prospective randomized trials have compared ICD implantation with other treatment modalities in patients with ARVC/D. ICD therapy is safe and effective in patients with ARVC/D and provides lifesaving protection. Due to the structural abnormalities of the RV myocardium in patients with ARVC/D, meticulous attention has to be paid to the placement of the RV defibril-
lation lead during lead implantation, in order to achieve satisfactory acute and long-term pacing and sensing results. Progression of myocardial atrophy and subsequent replacement by fat and fibrosis at the site of lead implantation may result in a loss of sensing function of the RV defibrillation lead and may require lead revision or the implantation of an additional pace/sense lead.\(^{40,51}\)

**Treatment of Heart Failure**

Symptomatic heart failure requiring treatment is present in only 10-20% of patients with ARVC/D. Symptomatic heart failure is unusual as an early manifestation of ARVC/D and occurs almost exclusively in patients with an advanced stage of the disease. In addition to progressive dysfunction of the RV, these patients frequently demonstrate LV involvement, and therefore exhibit clinical symptoms of biventricular heart failure. With the lack of causal treatment options for heart failure in ARVC/D, conventional pharmacologic therapy, including vasodilators, diuretics, beta-blockers, and digitalis is required. Some of the patients have undergone heart transplantation for intractable heart failure associated with ventricular tachyarrhythmias or a marked increase in the intracardiac defibrillation threshold in the presence of repeated episodes of VT.\(^{54,60,62}\)

**Management of Asymptomatic Patients With Family Members**

Asymptomatic patients with ARVC/D do not require specific treatment. However, they should be followed by regular non-invasive cardiac testing for the early detection of ventricular arrhythmias and the potential progression of the disease.\(^{13}\) Twelve-lead ECG and 2-D echocardiography represent essential baseline diagnostic investigations. Exercise testing, Holter monitoring, and signal-averaged ECG may be added to the previous essential studies. If the results of such testing reveal suspicious ARVC/D or complex ventricular arrhythmias, more detailed studies should be performed.\(^{52}\) Among the relatives of probands with ARVC/D, a minority fulfills diagnostic criteria for dilated cardiomyopathy without any evidence of RV disease.\(^{27}\)

**Exercise and ARVC/D**

ARVC/D is a frequent cause of sudden cardiac death in athletes.\(^{25}\) Patients with ARVC/D should be advised against participation in competitive sports, since this appears to be associated with accelerated disease progression and an increased risk of sudden death.\(^{14,49,52,53,56}\) Activities, such as golf or walking, are encouraged, whereas activities, such as marathon running or weight lifting, should be strongly discouraged.\(^{10}\) Sports activities, particularly running and bicycling, facilitate disruption of the myocardial cells at an earlier age.\(^{36}\) Recently, endurance training-induced RV enlargement has been reported in animal models.\(^{56}\)

**Overlap Between Brugada Syndrome and ARVC/D**

Among patients with ARVC/D, there is a subpopulation that exhibits a clinical and ECG pattern similar to that of patients with the Brugada syndrome.\(^{33,35,58}\) Endomyocardial biopsy showed typical fibrofatty infiltration of the myocardium in some patients with ECG features typical of the Brugada syndrome.\(^{57}\) Even ajmaline challenge showed positive results in some of the cases.\(^{58}\) Those cases are thought to represent an early or concealed form of the disease.

**Prognosis**

Long-term follow-up studies in large populations are not yet available, making the prognosis in asymptomatic patients difficult to define. There is even less information about the clinical outcome of asymptomatic, affected individuals. The limited data on risk stratification indicate that patients with severe RV dysfunction, LV involvement, a history of syncope or cardiac arrest, family history, and inducible VT are more prone to life-threatening VT and sudden death (Table 4). However, no prospective or randomized studies have investigated the comparative efficacy of these different treatment options in ARVC/D patients.\(^{39}\)

### Table 4. Proposed risk factors for unfavorable prognosis in arrhythmogenic right ventricular cardiomyopathy/dysplasia\(^{39}\)

<table>
<thead>
<tr>
<th>Clinical marker</th>
<th>Assessment</th>
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<tr>
<td>Previous cardiac arrest*</td>
<td>Clinical history</td>
</tr>
<tr>
<td>Syncope or sustained ventricular tachycardia</td>
<td>Direct inquiry regarding symptoms</td>
</tr>
<tr>
<td>with impairment of consciousness*</td>
<td></td>
</tr>
<tr>
<td>Increased QRS dispersion</td>
<td>A difference of ≥40 ms between the maximum and minimum QRS values occurring</td>
</tr>
<tr>
<td>Early onset of symptoms</td>
<td>in any of the 12 ECG leads</td>
</tr>
<tr>
<td>Severe right ventricular dilation</td>
<td>Direct inquiry regarding symptoms</td>
</tr>
<tr>
<td>Left ventricular involvement*</td>
<td>Regional wall motion abnormalities or dilation and impairment of systolic function in the left ventricle inverted T waves in the precordial leads beyond V1</td>
</tr>
</tbody>
</table>

*Clinical markers that warrant consideration of implantable cardioverter-defibrillator therapy
thus far.\textsuperscript{23}

As ARVC/D is a progressive disease that involves the RV, partially or globally, and becoming more diffusely damaged with time, the existence of RV failure implies progression and severity of the disease. Although macroscopic or histologic changes of the LV are found in many patients, LV failure is uncommon and it is present only in later stages of the disease. The biventricular failure mimics a dilated cardiomyopathy.\textsuperscript{10}

Conclusions

ARVC/D is a type of cardiomyopathy characterized by RV involvement and the risk of arrhythmic sudden death. Distinctive pathologic features are ventricular myocardial atrophy with replacement by fatty or fibrofatty tissue. Patients affected with ARVC/D should be excluded from competitive sports and vigorous training. Antiarrhythmic drugs may be used to suppress ventricular arrhythmias. However, recurrent arrhythmias from new foci are frequent during follow-up. ICD therapy has been increasingly used for secondary arrhythmias from new foci. Familial occurrence of ventricular tachyarrhythmias in patients with a low risk of sudden death. Cather ablation shows favorable acute results for eliminating ventricular arrhythmias. However, recurrent arrhythmias from new foci are frequent during follow-up, ICD therapy has been increasingly used for secondary and primary prevention of sudden death. Greater awareness and understanding of ARVC/D among physicians may prevent unnecessary deaths, especially in the young.

REFERENCES


