Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy
Guy Fontaine, M.D., Ph.D.,* Yves Gallais, M.D.,† Paul Fornes, M.D., Ph.D.,‡ Jean-Louis Hébert, M.D., Ph.D.,§ Robert Frank, M.D.¶

RIGHT ventricular dysplasia/cardiomyopathy is an inherited condition characterized by structural and functional abnormalities that involve mostly the right ventricle and sometimes the left ventricle as well. It is caused by the replacement of myocardial tissue by fat and fibrous tissue.¹ Males are involved more frequently.² The disease generally is discovered during adolescence, but pediatric cases have been reported.³ It manifests by means of a wide spectrum of clinical presentations, including mechanical myocardial dysfunction and various arrhythmias, generally of right ventricular origin, such as isolated extrasystoles, nonsustained or sustained ventricular tachycardia (VT), and ventricular fibrillation responsible for sudden death. The right atrium sometimes is dilated, which may explain atrial arrhythmias. These may be the first presenting arrhythmias. When ventricular arrhythmias are present, the disease is called arrhythmogenic right ventricular dysplasia (ARVD). Arrhythmias and congestive heart failure may be associated in the most severe forms of the disease.¹ Chest pain and tiredness are two recently identified symptoms of variable expression.

Since the first description of ARVD in 1977, there have been significant advances in the understanding of the etiopathogenesis, histopathology, clinical diagnosis, and treatment of this condition. ARVD has been added to the group of cardiomyopathies in a recent classification of the World Health Organization under the name of arrhythmogenic right ventricular cardiomyopathy. This term encompasses the multiple clinical forms of this condition.¹ Further studies are needed to improve our knowledge of the natural history of the disease, its risk-stratification, the mechanisms of chest pain, tiredness, and heart failure, and to improve the efficacy of therapy in improving heart failure, suppression of ventricular arrhythmias, and prevention of sudden death. Such studies require a large population. Currently, an International Registry is in development.

Genetics

Arrhythmogenic right ventricular dysplasia is a familial disease. The most common pattern of inheritance is autosomal dominant, with a penetrance in family members ranging from 20 to 35% in most countries, reaching 50% in the Veneto region of Italy.⁵ However, an autosomal recessive pattern also has been reported on the Greek island of Naxos, where dysplasia is associated with palmoplantar keratosis. In this condition, signs of the disease are more severe, and penetrance in family members is greater than 90%. The gene coding for plakoglobin, a protein involved in cellular adhesion, has been found recently to be responsible for the disease. This protein is likely to be responsible for both ventricular abnormalities and keratosis. However, the involvement of this gene has not been assessed in the common form of ARVD. There is no genetic test for its preclinical diagnosis.

Histology

The most striking morphologic feature of the disease is the diffuse or segmental loss of myocardium in the diaphragmatic and epicardial layers of the right ventricular free wall with replacement by fat and fibrous tissue.¹ Persisting strands of cardiomyocytes bordered by or embedded in a variable extent of fibrous tissue are observed inside fat. Only the subendocardial layers are preserved. These layers frequently are occupied by dissecting fibrous tissue. In contrast, the trabecular carne of the apex and the right side of the ventricular septum are hypertrophied, which explains some of the images obtained by contrast angiography.¹,⁶ Anterior, diaphragmatic, and posterior walls are involved, as well as some
parts of the septum and, to a lesser extent, the left ventricle.\textsuperscript{7} Aneurysmal dilatations are sometimes present at the apex, in the subtricuspid area, or in both. Infundibular dilatation is present in the most severe forms. Inflammation and a variable degree of fibrosis are observed in a large number of cases.

It is recognized now that the presence of fat intermixed with cardiomyocytes sometimes is observed in normal hearts. This recently discovered, purely adipose form seems independent of ARVD. It is characterized by partial or almost total replacement of the right ventricular wall by adipose tissue. In this case, there are no inflammatory infiltrates.\textsuperscript{8} This feature, called fat dissociation syndrome, seems specific to humans.\textsuperscript{9} In this condition, right ventricular dysfunction could be the main prognostic determinant when left ventricular impairment of various causes is also present.

### Etiopathogenesis

Arrhythmogenic right ventricular dysplasia has been observed in the fetus, but the first clinical signs generally are observed during adolescence.\textsuperscript{4} Loss of the right ventricular myocardium seems related to three possible basic mechanisms:

- Major replacement of myocardium by fat may be the result of early transdifferentiation of myoblasts into adipoblasts.
- Apoptosis or programmed cell death also has been shown in ARVD. However, massive destruction of cardiomyocytes and production of a relatively small amount of fat and fibrous tissue may represent its most severe form: the Uhl anomaly.
- Inflammatory phenomena generally are observed later in life. Cardiac arrhythmias can be triggered by activated neutrophils known to generate early after-depolarization.\textsuperscript{10} When inflammation is present, a spectrum of clinical presentations may be observed, including hyperacute myocarditis leading to fulminant heart failure or complete healing without clinical signs of heart dysfunction. This situation may be associated with additional fibrosis. In the severe forms of the disease, inflammatory changes generally involve both ventricles, producing an increased amount of “replacement” fibrous tissue. Currently, only Coxsackievirus has been found to be associated with these forms of ARVD with myocarditis.\textsuperscript{11}

### Epidemiology

The incidence and prevalence of ARVD is estimated at 1 in 10,000. Patients with a clinical diagnosis of ARVD based on appropriate symptoms, electrocardiographic changes, and right ventricular arrhythmias with both structural and functional right ventricular abnormalities represent only one end of the disease spectrum. A number of clinically unrecognized cases are not identified because these patients have no clear-cut symptoms or because sudden death occurs as the first manifestation of the disease, particularly in athletes. At the other end of the spectrum, patients with congestive heart failure with or without cardiac arrhythmias in whom the diagnosis of dysplasia was not recognized at an early stage of the disease might be given misdiagnoses of idiopathic dilated cardiomyopathy.\textsuperscript{12,13} The differences in prevalence observed in different places in the world could be because of clustering of the disease in some geographic areas, the fact that this condition currently is underrecognized, or both.

### Clinical Diagnosis

Standardized diagnostic criteria have been proposed by the Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology (Sophia-Antipolis, France) and by the Task Force of the Scientific Council on Cardiomyopathies of the World Heart Federation (Geneva, Switzerland). Diagnosis of ARVD is based on the presence of major and minor criteria encompassing structural, electrocardiographic, arrhythmic, and genetic factors. Among these criteria, inverted T waves beyond V\textsubscript{1} are a sign of diagnostic value that should attract attention, particularly in a young patient with a normal heart at physical examination. However, these criteria based on the opinion of experts have to be reconsidered on more objective grounds (table 1).

The recognition of mild, fruste, or localized forms of the disease remains a clinical challenge. It is difficult to diagnose ARVD in patients with minimal right ventricular abnormalities by echocardiographic or contrast angiographic examination. Magnetic resonance imaging is a promising technique in showing right ventricular anatomy and function as well as in characterizing the composition of the right ventricle wall, especially with regard to the presence of adipose tissue. However, its diagnostic sensitivity and specificity remain to be defined because the quality of images detected is currently interobserver dependent. The presence of signals suggesting fat in the right ventricle may be related to a latent form of the disease or to the dissociation of myocardial tissue by fat.\textsuperscript{9} Therefore, only the combination of magnetic resonance imaging signs, including size, function, and presence of fat in the free wall, is necessary to suggest diagnosis.

### Natural History

Clinically, prognosis of ARVD depends on both the electrical instability of the diseased myocardium and ventricular dysfunction leading to heart failure.
Cardiac arrhythmias can occur at any time during the disease course. Progressive loss of contractile tissue resulting in ventricular dysfunction and heart failure is the second important prognostic factor.7

Morphologically, the natural history of ARVD is characterized by (1) progressive replacement of myocardium by fat and fibrous tissue and, (2) in many cases, a superimposed inflammation process. After a concealed phase characterized by patchy distribution of fat in the right ventricle, progressive replacement of myocardium by fat and fibrous tissue creates an arrhythmogenic substrate, which is activated in some patients. When right ventricular involvement is severe, dysfunction occurs. At a later stage, left ventricular involvement by the same dysplastic process leads to congestive heart failure because of loss of left ventricular myocardium replaced by fat (biventricular dysplasia).

In some cases, myocarditis occurs during the disease progression. Both ventricles are involved, leading to an abrupt decrease in heart function. In these cases, the prognosis depends on the severity and extension of the intervening phenomenon.

These two situations of biventricular involvement by the initial disease process, superimposed myocarditis caused by environmental factors, or both lead to left ventricular dysfunction and, in their final stage, to “biventricular pump failure” and related complications. When cardiac arrhythmias are absent, ARVD may be misdiagnosed as an idiopathic dilated cardiomyopathy.12,15

**Therapy**

Currently, the clinical course of ARVD is not documented sufficiently, even in patients with overt disease and significant ventricular arrhythmia. Natural history of the asymptomatic affected family members is also unknown. Because the clinical signs that predict life-threatening cardiac arrhythmias, with the exception of cases of sudden death in family members, are known incompletely, there are no precise rules to select those patients who should require aggressive treatment. Moreover, the tests to assess the efficacy of pharmacologic and nonpharmacologic therapy in patients with ARVD need confirmation in a large series of patients. Therefore, there are no well-established guidelines in the treatment of patients, and the strategies are based largely on local experience gained at the different centers. Patients with non-life-threatening arrhythmias usually are treated empirically with antiarrhythmic drugs, including sotalol, β blockers, flecainide, propafenone, and amiodarone alone or in combination.14 Antiarrhythmic drug therapy guided by programmed ventricular stimulation with serial drug testing seems effective but is unable to prevent

Table 1. Criteria for ARVD/C Diagnosis

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<tr>
<th>Criteria</th>
<th>Major</th>
<th>Minor</th>
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<tr>
<td>Global or regional dysfunction and structural alterations*</td>
<td>Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) left ventricle impairment Localized right ventricular aneurysms (akinetidyskinetic areas of diastolic bulging)</td>
<td>Minor global right ventricular dilatation or ejection fraction reduction with normal left ventricle Mild segmental dilatation of the right ventricle</td>
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<tr>
<td>Repolarization abnormalities</td>
<td>Epsilon waves or localized prolongation (110 ms) of the QRS complex in precordial leads (V1, V2, or V3)</td>
<td>Regional right ventricular hypokinesia Inverted T waves in right precordial leads beyond V1 (people aged more than 12 yr; in absence of right bundle branch block)</td>
</tr>
<tr>
<td>Repolarization/conduction abnormalities</td>
<td>Late potentials (signal averaged electrocardiography)</td>
<td>Frequent ventricular extrasystoles with left bundle branch block morphology (more than 1,000/24 h; Holter)</td>
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<tr>
<td>Arrhythmias</td>
<td>Sustained left bundle branch block type ventricular tachycardia (electrocardiography, Holter, exercise testing)</td>
<td>Familial history of premature sudden death (&lt; 35 yr) caused by suspected right ventricular dysplasia</td>
</tr>
<tr>
<td>Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
<td>Familial history (clinical diagnosis based on current criteria)</td>
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* Detected by echocardiography, angiography, magnetic resonance imaging, or radionuclide scintigraphy. ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy.


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sudden death in all cases. Catheter ablation is reserved to those patients with inducible, stable, multiple monomorphic ventricular arrhythmias in whom drug therapy either proves ineffective or is associated with serious side effects or too frequent recurrences. Implantation of a defibrillator seems appropriate when the VT occurrences are life-threatening, as well as in survivors of cardiac arrest when the VT high rate leads to hemodynamic compromise. The device also is used prophylactically in familial cases of sudden death in close relatives or when electrophysiologic-guided drug therapy is not applicable because of the inability to reproducibly induce a stable VT during electrophysiologic studies. However, implantable defibrillators, which are the only effective safeguard against sudden death, need to be evaluated in a large series of patients. Irreversible cases of sudden death in apparently normal hearts have been explained by pathologic examination. In case of heart failure, right ventricular cardiomyoplasty, multisite pacing, and heart transplantation might be considered.

ARVD-related Irreversible Cardiac Arrest during Anesthesia Despite Intensive Medical Attention

In this issue of Anesthesiology, Houfani et al.15 report two children who died suddenly 4 and 30 hours after surgery, respectively, despite the efforts of well-trained anesthesiologists and a well-trained surgical team. In a series of 1,700 forensic autopsies performed in sudden death cases recorded between 1981 and 1997 in Lyon, France, the authors found 50 irreversible cardiac arrests during surgery for benign disease. During autopsy, it was found that 47 patients had a cardiac pathology. Of those, 18 (36%) had histologic signs of ARVD.16

The author (G. F.) has examined the case of a 23-yr-old woman who died of irreversible cardiac arrest during induction of anesthesia for anal fistula related to Crohn disease. Autopsy revealed a typical histologic feature of ARVD. This patient was classified as American Society of Anesthesiologists physical status I; therefore, preoperative electrocardiography was not performed. This case and that of Houfani et al.15 have in common histologic signs of myocardial inflammation. These signs are frequent in the myocardium of both ventricles in ARVD. They also may be a cause of triggered arrhythmias. However, it seems too speculative to relate the irreversibility of cardiac arrest to inflammation.

Practical Consequences

Electrocardiographic signs that may attract attention to ARVD are inverted T waves in right precordial leads; QRS prolongation greater than 110 ms; extrasystoles with a left bundle branch block pattern; history of palpitations associated with neurologic signs of obviously nonvasovagal origin; and cases of sudden death, syncope, or both in close family members, especially if sudden death occurred in a young adult, regardless of the presumed cause. In the absence of an emergency, ARVD investigation by noninvasive techniques, invasive techniques, or both have to be performed, first by electrophysiologic techniques and later confirmed by contrast angiography.

Anesthesiology and Arrhythmias

In the two reported postoperative cases by Houfani et al.,15 anesthesia seems not to be involved. In our case, propofol was suspected to be involved. However, most of the anesthetics commonly used in France, including isoflurane, desflurane, sevoflurane, enfurane, ketamine, etomidate, propofol, and thiopentone, have no or minor arrhythmogenic effects.17

In our cardiology department, more than 200 ARVD patients originally referred for severe arrhythmias have been anesthetized for ablative procedures or external DC shock without cardiac arrest. This complication might have been prevented by previous chronic treatment by antiarrhythmic drugs, including sotalol in 50% of the cases, other β-adrenergic antagonists in 20% of the cases, amiodarone 20% of the time, and flecainide 10% of the time. These drugs have been used alone or in combination in the most severe cases, particularly amiodarone plus β-adrenergic antagonists. However, the situation in our center should be considered in light of the particular selection of patients with established diagnoses of ARVD who submitted to the ablation procedure in whom the problem is to induce a well-tolerated, stable, not-too-fast VT to permit precise mapping for ablation. Therefore, chronic amiodarone treatment is maintained, but β-adrenergic antagonist administration is interrupted a few days before the procedure.

Sedation usually is accomplished with use of midazolam and alfentanil. When general anesthesia with tracheal intubation and controlled ventilation is needed, we use a continuous infusion of propofol, vecuronium, and alfentanil.

When an undiagnosed patient presents with ventricular arrhythmias, such as polymorphic extrasystoles or short or sustained life-threatening VT, an elective surgical procedure should be delayed or cancelled until the arrhythmia is controlled. In this case, intravenous amiodarone is the drug of first choice because of its proven efficacy in the control of out-of-hospital cardiac arrest.19 The common starting dose is 150 mg injected intravenously in 20 min. Depending on the severity of hypotension, ephedrine, dobutamine, and epinephrine may be used. It is of note that intravenous amiodarone also might be useful when
arrhythmias are induced by epinephrine, as suggested in the case reported in this issue of Anesthesiology. When hypertension is present, isoflurane, nicardipine, and, in case of sinus tachycardia, a short-acting β-adrenergic antagonist, such as esmolol, are appropriate.

The International Registry

A registry has been established by the Task Force of the Scientific Council on Cardiomyopathies of the World Heart Federation and by the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology to gather needed information regarding ARVD. It likely will contribute to a better knowledge of this disease and its variants.

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References