

## REVIEW ARTICLE

John A. Jarcho, M.D., *Editor*

# Arrhythmogenic Right Ventricular Cardiomyopathy

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**A**RRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC), ALSO known as arrhythmogenic right ventricular dysplasia, is a heritable heart-muscle disorder that predominantly affects the right ventricle. Progressive loss of right ventricular myocardium and its replacement by fibrofatty tissue is the pathological hallmark of the disease.<sup>1</sup> ARVC is one of the leading causes of arrhythmic cardiac arrest in young people and athletes. Since the original report by Marcus and colleagues was published in 1982, describing 24 affected patients,<sup>2</sup> there have been substantial advances in our understanding of the pathogenesis, clinical manifestations, and long-term outcome of the disorder. The disease was initially designated as a dysplasia because it was thought to be a congenital defect in the development of the right ventricular myocardium. The subsequent discovery that the disease is caused by a genetic defect in the cardiac desmosomes has led to its recognition as a cardiomyopathy and its inclusion in the classification of cardiomyopathies by the American Heart Association.<sup>3</sup> This article focuses on our current understanding of the pathogenesis of ARVC, as well as diagnostic criteria and approaches to risk stratification and therapy.

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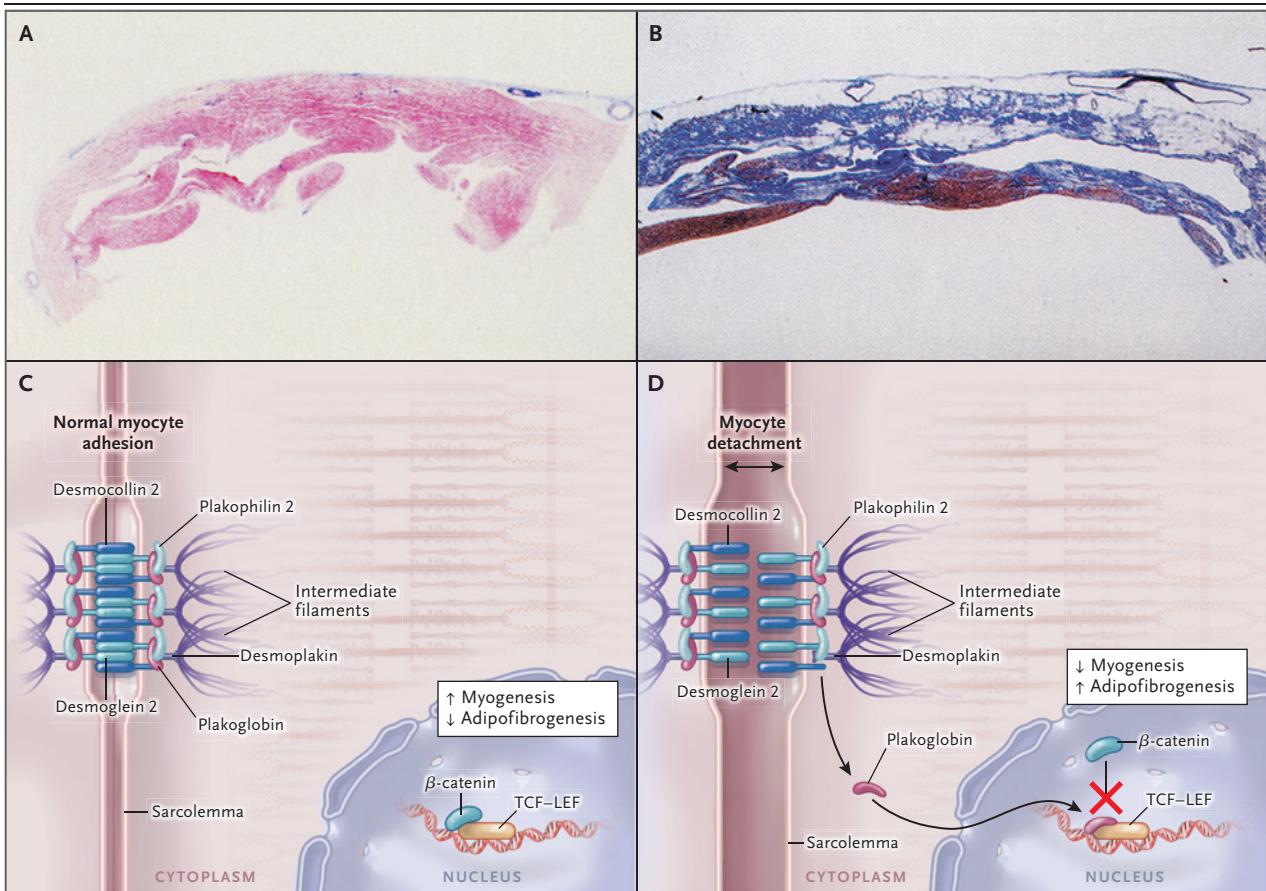
## PATHOGENESIS

**PATHOLOGICAL FEATURES**

The distinctive histopathological feature of ARVC is the loss of right ventricular myocardium, with the substitution of fibrous and fatty tissue (Fig. 1A and 1B).<sup>4</sup> Patchy inflammatory infiltrates (mainly T lymphocytes) are often observed in association with dying myocytes, suggesting that the pathologic process may be immunologically mediated.<sup>4,5</sup> The fibrofatty scar tissue progresses from the epicardium toward the endocardium and predominantly involves the right ventricular free wall, resulting in wall thinning and aneurysmal dilatation, which are typically localized in the inflow tract (subtricuspid region), outflow tract (infundibular region), and apex (“triangle of dysplasia”).<sup>2,4</sup> In the typical form of ARVC, the left ventricle is affected to a lesser extent than the right ventricle; however, there are disease variants characterized by equivalent or even predominant involvement of the left ventricle.<sup>5</sup>

**MOLECULAR GENETIC FEATURES**

Mutations in the genes encoding desmosomal proteins, which are important in cell-to-cell adhesion, play a key role in the pathogenesis of ARVC. The characterization of ARVC as a cell-adhesion disorder was first suggested by a molecular genetic study involving patients with Naxos disease.<sup>6</sup> This disease is an autosomal recessive cardiocutaneous syndrome characterized by cosegregation of abnormalities of the heart (ARVC), skin (palmoplantar keratosis), and hair (woolly hair). The



**Figure 1. Histopathological Features and Pathogenesis of Arrhythmogenic Right Ventricular Cardiomyopathy.**

The distinctive histopathological feature of arrhythmogenic right ventricular cardiomyopathy (ARVC) is the loss of right ventricular myocardium and the substitution of fibrous and fatty tissue. Panel A shows a full-thickness histologic section (azan trichrome stain) of the anterior right ventricular wall in a normal heart; Panel B shows a similar section from the heart of a patient with ARVC who died suddenly. With the azan trichrome stain, myocytes appear red, fibrous tissue appears blue, and fatty tissue appears white. ARVC is caused by genetically defective desmosomes, which are cell-to-cell adhesive structures. The desmosome contains three major components: desmoplakin, which binds to intermediate filaments (i.e., cardiac desmin); transmembrane proteins (i.e., desmosomal cadherins), including desmocollin 2 and desmoglein 2; and linker proteins (i.e., proteins of the armadillo family), including plakoglobin and plakophilin 2, which mediate interactions between the desmosomal cadherin tails and desmoplakin, as shown in Panel C. Abnormal desmosomes confer a predisposition over time to disruption of the intercellular junction, as shown in Panel D (double-headed arrow), mostly under conditions of increased mechanical stress, such as sports activity. A parallel pathogenic mechanism involves the canonical Wnt- $\beta$ -catenin signaling pathway. This evolutionarily conserved pathway plays a pivotal role in cardiac development, myocyte differentiation, and normal myocardial architecture. During canonical Wnt- $\beta$ -catenin signaling,  $\beta$ -catenin forms complexes with members of the TCF-LEF (T-cell factor-lymphocyte-enhancing factor) family of transcription factors in the nucleus to prevent the differentiation of mesodermal precursors into adipocytes and fibrocytes by suppressing the expression of adipogenic and fibrogenic genes (Panel C). Impairment of desmosomal assembly by genetically defective proteins causes the translocation of plakoglobin from the sarcolemma to the nucleus (arrows in Panel D), where it may antagonize the effects of  $\beta$ -catenin. By competing with  $\beta$ -catenin, intranuclear plakoglobin suppresses Wnt- $\beta$ -catenin signaling and induces a gene transcriptional switch from myogenesis to adipogenesis and fibrogenesis (Panel D). Panels A and B are reprinted from Thiene et al.<sup>1</sup>

concurrency of epidermal and myocardial abnormalities in Naxos disease is explained by the fact that these two types of tissue have similar junction structures.<sup>7</sup> Mutations in the gene encoding plakoglobin (JUP) were the first disease-causing

variants to be identified in patients with Naxos disease.<sup>6</sup> Plakoglobin is a major constituent of desmosomal complexes.

Mutations in genes encoding other desmosomal proteins were subsequently shown to

cause the more common (nonsyndromic) autosomal dominant form of ARVC. These proteins include desmoplakin (DSP),<sup>8</sup> plakophilin 2 (PKP2),<sup>9</sup> desmoglein 2 (DSG2),<sup>10</sup> and desmocollin 2 (DSC2).<sup>11</sup> A recessive mutation in the DSP gene was shown to cause another cardiocutaneous syndrome, the Carvajal syndrome.<sup>12</sup> Autosomal dominant ARVC has also been linked to rare pathogenic mutations in genes unrelated to cell-to-cell junctional apparatus.<sup>13</sup>

#### **PATHOPHYSIOLOGICAL FEATURES**

Ultrastructural studies of myocardial-biopsy samples obtained from patients with ARVC have shown intercalated disk remodeling with abnormalities and loss of desmosomes.<sup>14</sup> These findings support the theory that genetically abnormal desmosomes lead to disruption of intercellular junctions, with myocyte detachment and cell death (Fig. 1C and 1D). Mechanical uncoupling of myocytes may be aggravated by physical exercise, which increases pressure, afterload, and wall stress to a disproportionately greater extent in the right ventricle than in the left ventricle.<sup>15</sup> However, studies of myocytes from transgenic mice expressing mutant desmosomal proteins have failed to show a reduction in cell-to-cell adhesion, raising questions about the pathogenic role of the altered integrity of the intercellular junction.<sup>16</sup>

In addition to being specialized structures that provide mechanical cell attachment, desmosomes are important mediators of intracellular and intercellular signal transduction. Elegant immunohistochemical studies have shown that the mutant form of the plakoglobin protein fails to integrate into desmosomes and shifts from intercalated disks to cytosol and nuclear pools, where it causes changes in nuclear signaling and transcriptional activity, in particular through pathways regulated by the protein  $\beta$ -catenin.<sup>17</sup> Studies in DSP-deficient mice indicate that the inhibition of the canonical Wnt- $\beta$ -catenin signaling pathway induced by nuclear translocation of plakoglobin may increase the expression of adipogenic and fibrogenic genes and contribute to the development of fibrofatty myocardial scarring (Fig. 1C and 1D).<sup>18</sup>

The fibrofatty tissue that replaces myocardium in ARVC is thought to contribute to the development of ventricular arrhythmias by slowing intraventricular conduction and acting as a substrate

for arrhythmias through a scar-related macro-reentry mechanism, similar to that observed after myocardial infarction.<sup>19</sup> Life-threatening ventricular arrhythmias in ARVC may also be the result of mechanisms operating at the molecular and cellular levels. Desmosomes, sodium channels, and gap-junction proteins interact synergistically to regulate adhesion, excitability, and coupling of myocytes; this coordinated network of proteins located at the intercalated disks has been termed the “connexome.”<sup>20</sup> Loss of expression of desmosomal proteins may cause (or contribute to) potentially fatal arrhythmias by inducing gap-junction remodeling, with reduction of total content and substantial redistribution of the gap-junction protein connexin 43, and decreasing the amplitude and kinetics of the sodium current.<sup>21-23</sup>

The Brugada syndrome is a cardiac ion-channel disorder caused by a genetic deficiency in sodium-channel function. There is some evidence that the Brugada syndrome and ARVC may share clinical features and arrhythmic mechanisms as a result of their common origin from the connexome.<sup>24</sup>

Sports activity increases the risk of sudden cardiac death among adolescents and young adults with ARVC.<sup>1,25</sup> Physical exercise may aggravate mechanical uncoupling of myocytes; it may also trigger malignant ventricular arrhythmias and is a critical environmental factor in the promotion of the development and progression of the disease. The key role of exercise as a disease modifier was suggested by both experimental studies of transgenic plakoglobin-deficient mice and clinical studies of affected patients with and those without desmosomal gene mutations.<sup>26-28</sup>

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#### **CLINICAL FEATURES AND DIAGNOSIS**

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##### **EPIDEMIOLOGY**

The prevalence of ARVC is estimated to range from 1 case in 5000 persons in the general population to 1 in 2000 in some European countries such as Italy and Germany.<sup>29,30</sup> Approximately 50% of affected patients have a positive family history, but both incomplete penetrance and limited phenotypic expression are common and probably account for underestimation of the prevalence of familial disease. The disease is typically transmitted with an autosomal dominant pattern of inheritance, although rare auto-

somal recessive forms have been described.<sup>31</sup> The disease is more malignant in men than in women, a finding that can be explained either by a direct influence of sex hormones on the mechanisms involved in the phenotypic expression of the disease<sup>32,33</sup> or by sex-based differences in the amount or intensity of exercise.<sup>27</sup>

#### CLINICAL PRESENTATION AND NATURAL HISTORY

ARVC typically becomes clinically apparent between the second and fourth decades of life.<sup>32-37</sup> Clinically overt disease is preceded by a preclinical phase, which is characterized by minimal or no structural abnormalities (“concealed disease”). Sudden cardiac death may be the first clinical manifestation of the disease. In a study in the Veneto region of Italy, 20% of deaths in young people and athletes were caused by previously undiagnosed ARVC.<sup>1</sup>

The most common clinical presentation is palpitations or effort-induced syncope in an adolescent or young adult, with T-wave inversion in the right precordial leads (V<sub>1</sub> through V<sub>4</sub>) on the electrocardiogram, ventricular arrhythmias with a left bundle-branch block pattern, and right ventricular abnormalities on imaging tests. Electrocardiographic depolarization abnormalities, which reflect defective conduction through the diseased right ventricular myocardium, may also be present (Fig. 2).<sup>38-40</sup> Ventricular arrhythmias range from frequent premature ventricular beats to ventricular tachycardia, which may degenerate into ventricular fibrillation; the arrhythmias are characteristically triggered or worsened by adrenergic stimulation.<sup>1,5,34,41</sup> Diagnostic alterations of the right ventricle on imaging studies consist of global dilatation and dysfunction and regional wall-motion abnormalities such as systolic akinesia or dyskinesia or diastolic bulging; the left ventricle and the septum are usually involved to a lesser extent, if at all.<sup>42-44</sup> Cardiac magnetic resonance imaging (MRI) has become the preferred imaging technique because it combines the evaluation of structural and functional ventricular abnormalities with noninvasive tissue characterization with the use of late gadolinium enhancement, which provides information about the presence and amount of fibrofatty myocardial scarring.<sup>44,45</sup>

End-stage right ventricular or biventricular pump failure may develop in patients with longstanding disease.<sup>5,46</sup> Genotype–phenotype corre-

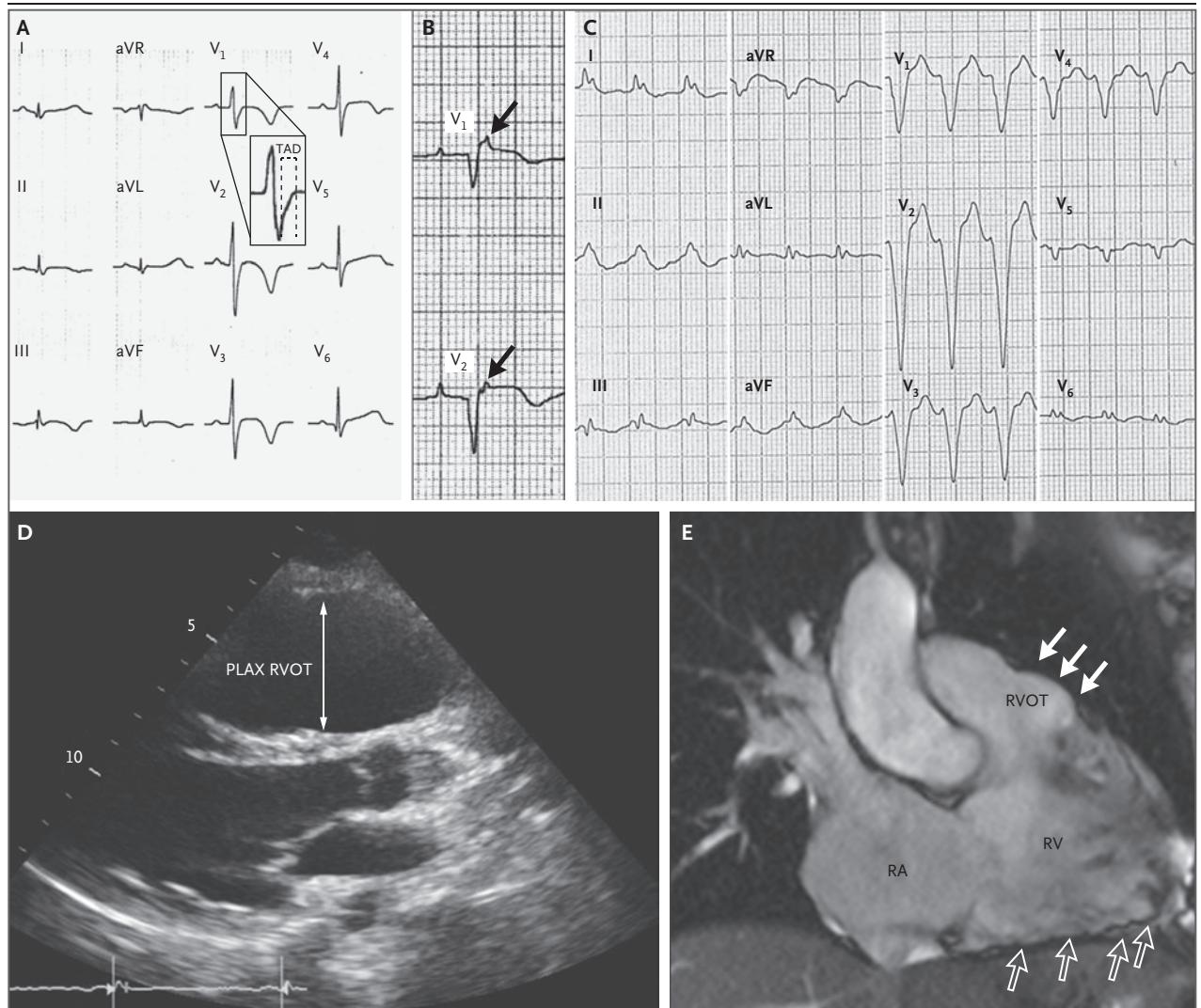
lation studies and the increasing use of cardiac MRI have identified clinical variants characterized by early left ventricular involvement, especially among patients with DSP gene mutations,<sup>33</sup> which may either parallel or exceed the severity of right ventricular disease.<sup>47</sup> Clinical features of left-sided variants include inverted T waves in the inferolateral leads, ventricular arrhythmias with a right bundle-branch block, left ventricular dilatation and dysfunction, and late gadolinium enhancement of the left ventricular wall with a subepicardial or midmyocardial distribution. These findings support the concept that ARVC can be a biventricular muscle disease (i.e., a disease involving the myocardium of both ventricles) and have led some to use the broader term “arrhythmogenic cardiomyopathy.”<sup>47</sup>

#### CLINICAL DIAGNOSIS

To standardize the clinical diagnosis of ARVC, in 1994 an international task force proposed guidelines in the form of a qualitative scoring system with major and minor criteria.<sup>48</sup> In 2010, the task force revised the guidelines to improve diagnostic sensitivity, mostly for the clinical screening of family members, by providing quantitative criteria for diagnosing right ventricular abnormalities and adding molecular genetic criteria (Table 1).<sup>49</sup> However, the diagnosis remains problematic because of the low specificity of electrocardiographic abnormalities, multiple causes of right ventricular arrhythmias, difficulties in the use of imaging to assess right ventricular structure and function, and the sometimes puzzling results of genetic testing.

The diagnosis is particularly challenging in children, because clinical manifestations of early ARVC are subtle. Cardiac MRI has proved to be more sensitive than echocardiography for detecting early ventricular dilatation and dysfunction in children.<sup>45</sup>

Conditions that may be difficult to differentiate from ARVC include idiopathic right ventricular outflow-tract tachycardia, cardiac sarcoidosis, and congenital heart disease leading to right ventricular volume overload.<sup>50,51</sup> Biventricular variants of the disease with severe left ventricular involvement may be indistinguishable from dilated cardiomyopathy. The difficult differential diagnosis, together with referral bias, may account for the discrepancies in the reported incidence of heart failure in patients with ARVC.<sup>5,46,52</sup>



**Figure 2. Electrocardiographic and Imaging Features of ARVC.**

The 12-lead standard electrocardiogram in Panel A shows a repolarization abnormality that is characteristic of ARVC, with negative T waves in leads V<sub>1</sub> through V<sub>4</sub> and depolarization changes, including low QRS voltages (<0.5 mV) in the limb leads and prolongation of the right precordial QRS complex, with a delayed S-wave upstroke. The terminal activation duration (TAD), which is the interval between the nadir of the S wave and the end of all depolarization deflections, is prolonged, at 80 msec, in lead V<sub>1</sub> (inset); the normal value is less than 55 msec. Panel B shows an example of “epsilon waves” (i.e., small-amplitude distinct potentials between the end of the QRS complex and the beginning of the T wave) in leads V<sub>1</sub> and V<sub>2</sub>. This is a highly specific electrocardiographic abnormality that is seen in a minority of patients with advanced disease. The 12-lead standard electrocardiogram in Panel C shows ventricular tachycardia (160 beats per minute) with a left bundle-branch block pattern. The two-dimensional echocardiogram, parasternal long-axis view (PLAX), in Panel D shows dilatation of the right ventricular outflow tract (RVOT), at 38 mm (normal value, <32 mm). The cardiac MRI scan (systolic frame of right ventricular two-chamber long-axis view on cine sequences) in Panel E shows an aneurysm of the RVOT (solid arrows) and multiple sacculations of the inferior and apical regions (open arrows). RA denotes right atrium, and RV right ventricle.

#### PRECLINICAL DIAGNOSIS BY GENOTYPING

On the basis of pooled data from major studies of molecular genetic screening for desmosomal gene mutations, the estimated overall rate of successful genotyping among patients meeting the diagnostic criteria for ARVC established by

the international task force is approximately 50%.<sup>32,33,53,54</sup> The most commonly affected gene is *PKP2* (in 10 to 45% of patients), followed by *DSP* (10 to 15%), *DSG2* (7 to 10%), and *DSC2* (2%). Screening of nondesmosomal genes only marginally affects the detection rate for mutations.

**Table 1. International Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy.\***

Category	Major Criteria	Minor Criteria
Global or regional dysfunction and structural alteration†		
On two-dimensional echocardiography	Regional RV akinesia, dyskinesia, or aneurysm and one of the following (end diastole): PLAX RVOT $\geq 32$ mm ( $\geq 19$ mm per square meter when corrected for body-surface area), PSAX RVOT $\geq 36$ mm ( $\geq 21$ mm per square meter when corrected for body-surface area), or fractional area change of $\leq 33\%$	Regional RV akinesia or dyskinesia and one of the following (end diastole): PLAX RVOT 29 to $<32$ mm (16 to $<19$ mm per square meter when corrected for body-surface area), PSAX RVOT 32 to $<36$ mm (18 to $<21$ mm per square meter when corrected for body-surface area), or fractional area change of 34 to 40%
On MRI	Regional RV akinesia or dyssynchronous RV contraction and one of the following: ratio of RV end-diastolic volume to body-surface area $\geq 110$ ml per square meter (male patients) or $\geq 100$ ml per square meter (female patients), or RV ejection fraction $\leq 40\%$	Regional RV akinesia or dyssynchronous RV contraction and one of the following: ratio of RV end-diastolic volume to body-surface area 100 to $<110$ ml per square meter (male patients) or 90 to $<100$ ml per square meter (female patients), or RV ejection fraction 41 to 45%
On RV angiography	Regional RV akinesia, dyskinesia, or aneurysm	
Tissue characterization	$<60\%$ residual myocytes on morphometric analysis (or $<50\%$ , if estimated) and fibrous replacement of the RV free-wall myocardium, with or without fatty replacement of tissue, in at least one endomyocardial-biopsy sample	60 to 75% residual myocytes, on morphometric analysis (or 50 to 65%, if estimated) and fibrous replacement of the RV free-wall myocardium, with or without fatty replacement of tissue, in at least one endomyocardial-biopsy sample
Repolarization abnormalities	Inverted T waves in right precordial leads (V <sub>1</sub> , V <sub>2</sub> , and V <sub>3</sub> ) or beyond in patients older than 14 yr of age (in the absence of complete right bundle-branch block, QRS $\geq 120$ msec)	Inverted T waves in leads V <sub>1</sub> and V <sub>2</sub> in patients older than 14 yr of age (in the absence of complete right bundle-branch block) or in V <sub>4</sub> , V <sub>5</sub> , or V <sub>6</sub> ; inverted T waves in leads V <sub>1</sub> , V <sub>2</sub> , V <sub>3</sub> , and V <sub>4</sub> in patients older than 14 yr of age (in the presence of complete right bundle-branch block)
Depolarization and conduction abnormalities	Epsilon wave (reproducible low-amplitude signals from end of QRS complex to onset of the T wave) in the right precordial leads (V <sub>1</sub> , V <sub>2</sub> , and V <sub>3</sub> )	Late potentials on signal-averaged ECG in at least one of three parameters in the absence of a QRS complex duration of $\geq 110$ msec on the standard ECG; filtered QRS complex duration, $\geq 114$ msec; duration of terminal QRS complex $<40$ $\mu$ V (low-amplitude signal duration), $\geq 38$ msec; root-mean-square voltage of terminal 40 msec, $\leq 20$ $\mu$ V; terminal activation duration of QRS complex, $\geq 55$ msec, measured from the nadir of the S wave to the end of the QRS complex, including R', in V <sub>1</sub> , V <sub>2</sub> , or V <sub>3</sub> , in the absence of complete right bundle-branch block
Arrhythmias	Nonsustained or sustained ventricular tachycardia with a left bundle-branch block and superior axis pattern (negative or indeterminate QRS complex in leads II, III, and aVF and positive QRS complex in lead aVL)	Nonsustained or sustained ventricular tachycardia of RV outflow configuration with a left bundle-branch block and inferior axis pattern (positive QRS complex in leads II, III, and aVF and negative QRS complex in lead aVL) or unknown axis, or $>500$ ventricular extrasystoles per 24 hr (on Holter monitoring)
Family history	ARVC confirmed in a first-degree relative who meets current task-force criteria, ARVC confirmed pathologically at autopsy or surgery in a first-degree relative, or identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation‡	History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether current task-force criteria are met, premature sudden death (at $<35$ yr of age) due to suspected ARVC in a first-degree relative, or ARVC confirmed pathologically or by current task-force criteria in a second-degree relative

\* The table is adapted from Marcus et al.<sup>49</sup> The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is considered to be definite if the patient meets two major criteria, one major and two minor criteria, or four minor criteria from different categories; the diagnosis is considered to be borderline if the patient meets one major and one minor criteria or three minor criteria from different categories, and the diagnosis is classified as possible if the patient meets one major or two minor criteria from different categories. ECG denotes electrocardiogram, PLAX parasternal long-axis view, PSAX parasternal short-axis view, RV right ventricular, and RVOT RV outflow tract.

† Hypokinesia is not included in this or subsequent definitions of RV regional wall-motion abnormalities for the proposed modified criteria.

‡ A pathogenic mutation is a DNA alteration associated with ARVC that alters or is expected to alter the structure or function of the protein or has shown linkage to the disease phenotype in a conclusive pedigree (i.e., a pedigree providing conclusive evidence of a mendelian inheritance of the disease phenotype).

Clinically, genotyping is most often used to identify a mutation that is considered likely to be causal in a proband who fulfills phenotypic diagnostic criteria, and thus to identify gene carriers among family members by means of mutation-specific genetic testing.<sup>55</sup> Genotyping to confirm the diagnosis in an isolated patient with a borderline or questionable phenotype is not indicated on a routine basis. The true prevalence of disease-causing mutations has yet to be determined. Therefore, a negative genetic test does not exclude the possibility that the phenotype is due to a mutation of an unknown disease-causing gene.

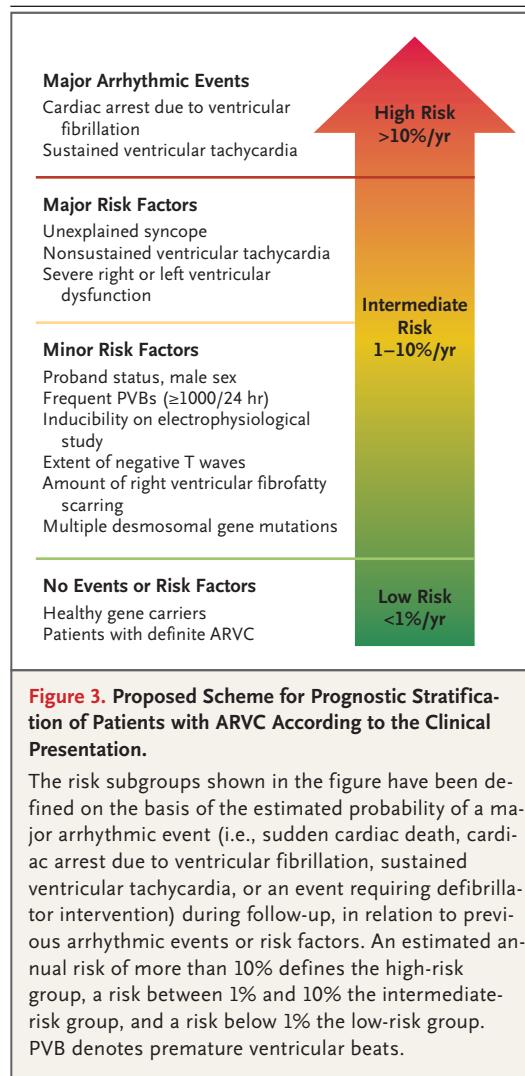
On the other hand, the interpretation of an apparently positive genetic test for ARVC is made more challenging by the difficulty in differentiating causative mutations, especially missense mutations, from nonpathogenetic variants and polymorphisms, mainly because of the lack of functional or biologic studies that confirm the pathogenetic effects of gene variants. It has been reported that 16% of healthy persons have missense mutations in one of the major ARVC susceptibility genes.<sup>56</sup> The prognostic value of genotyping also remains to be elucidated. Data indicate that patients with multiple desmosomal gene mutations are likely to have a more severe phenotype and may have an increased lifetime risk of malignant arrhythmias and sudden cardiac death.<sup>32,33</sup>

The results of commercially available genetic tests for ARVC should be evaluated cautiously, and genetic counseling is recommended for assistance in test interpretation.<sup>31,55</sup> Otherwise, critical information regarding the complexity of genetic data and their limitations for clinical diagnosis and prognosis may not be made clear when the results of such tests are reported.

## PROGNOSIS AND TREATMENT

### RISK STRATIFICATION

The clinical course of ARVC is characterized by the occurrence of arrhythmic events, which can cause sudden death, and the impairment of biventricular systolic function, which can lead to death from heart failure. The estimated overall mortality varies among studies, ranging from 0.08 to 3.6% per year.<sup>52</sup> The mortality was initially overestimated because it was based on studies at tertiary referral centers, which predominantly included high-risk patients. Recent



studies of community-based patient cohorts have shown that the long-term outcome for treated index patients and family members is favorable (annual mortality, <1%).<sup>35-37</sup>

The prognosis for patients with ARVC depends largely on the severity of arrhythmias and ventricular dysfunction (Fig. 3).<sup>52,57-62</sup> Prior cardiac arrest due to ventricular fibrillation and sustained ventricular tachycardia are the most important predictors of life-threatening arrhythmic events during follow-up. Major risk factors include unexplained syncope, nonsustained ventricular tachycardia on ambulatory monitoring or exercise testing, and severe systolic dysfunction of the right ventricle, left ventricle, or both.<sup>60,61</sup> Several minor risk factors have been identified, but their association with an unfavorable out-

come is based on either limited scientific evidence or conflicting data.<sup>52,57</sup> Although intracardiac electrophysiological testing has traditionally been used to assess the risk of ventricular arrhythmias, the prognostic value of ventricular tachycardia or ventricular fibrillation induced by programmed ventricular stimulation in patients with asymptomatic ARVC remains unclear.<sup>60,62</sup>

#### THErapy

The aims of clinical management of ARVC are to reduce the risk of sudden cardiac death and improve the quality of life by alleviating arrhythmic and heart-failure symptoms. Restriction from intense sports activity is regarded as an important preventive tool for both healthy gene carriers and clinically affected persons in order to protect them from the risk of exercise-related malignant arrhythmic events and disease development or progression.<sup>52,63</sup> The available evidence indicates that family members with a negative phenotype (either healthy gene carriers or those with an unknown genotype) do not need any specific treatment other than sports restriction; however, lifelong clinical assessment with the use of noninvasive tests at least every 2 years is warranted because of the age-related penetrance and progressive nature of ARVC.

Despite limited supportive data, beta-blockers are currently recommended for all clinically affected persons, for both prevention of arrhythmias and reduction of right ventricular wall stress.<sup>52</sup> In patients with ventricular arrhythmias, antiarrhythmic drug therapy offers the potential to ameliorate symptoms, although there is no proof that it confers protection against sudden cardiac death. Amiodarone, alone or in association with beta-blockers, and sotalol are the most effective drugs, combining the synergistic effects of class III antiarrhythmic properties and beta-adrenergic blockade.<sup>58,59,64</sup> The potential for serious cumulative toxic effects precludes long-term therapy with amiodarone, especially in younger patients.

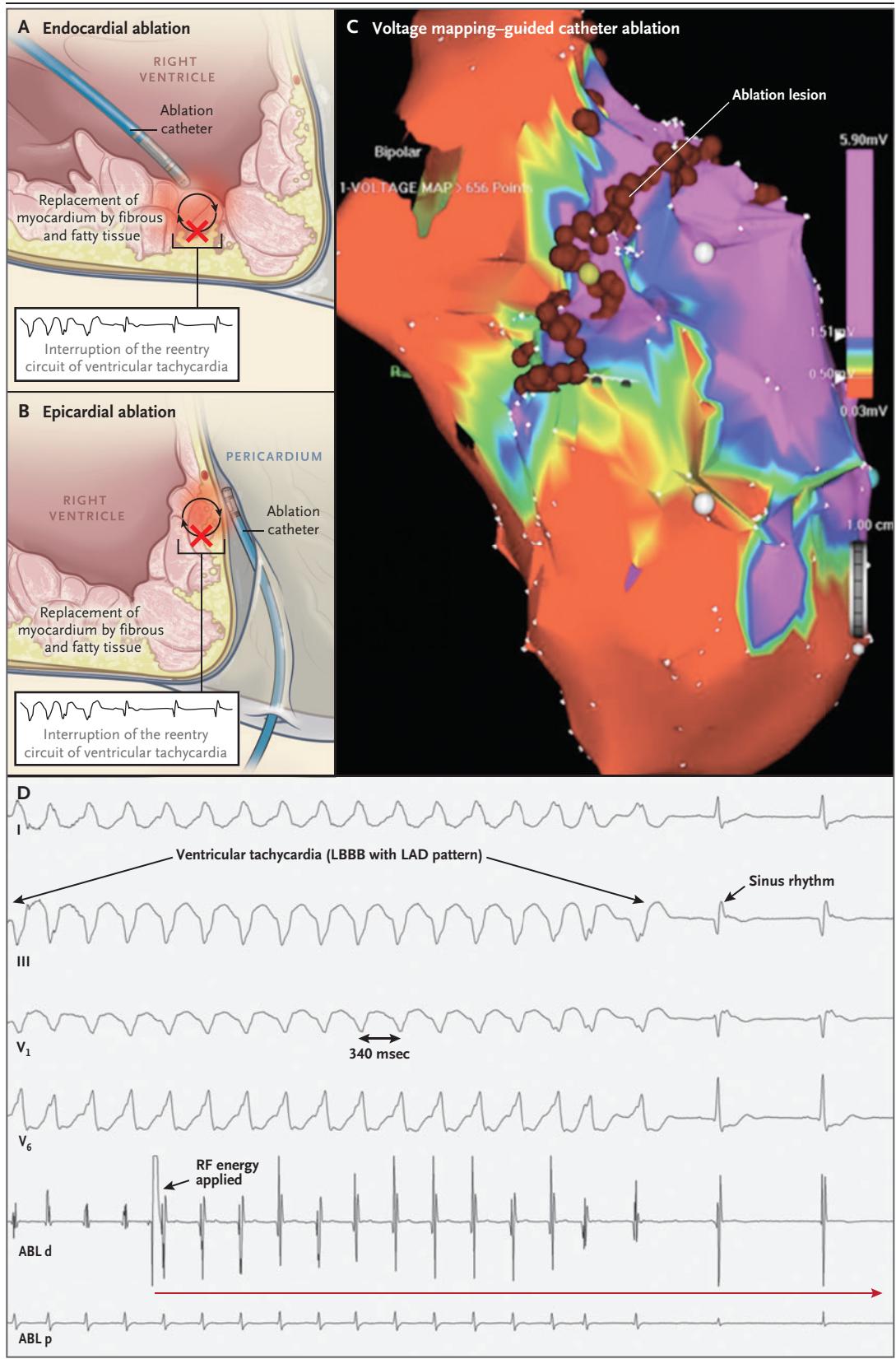
Catheter ablation is a therapeutic option for patients who have episodes of sustained, monomorphic ventricular tachycardia (Fig. 4). However, it should be regarded as a palliative rather than curative therapeutic approach because of the high frequency of subsequent recurrences of ventricular tachycardia and the unproven efficacy of ablation as a means of preventing sudden cardiac

#### Figure 4 (facing page). Catheter Ablation of Ventricular Tachycardia in Patients with ARVC.

In patients with ARVC, ventricular tachycardia may be treated by means of catheter ablation with the use of either an endocardial or an epicardial approach, depending on the site of the arrhythmia substrate. For endocardial ablation (Panel A), the catheter is advanced into the right ventricular cavity through the venous system; the black circular arrow shows a reentry circuit of ventricular tachycardia, and the red X indicates interruption by endocardial catheter ablation of the reentry circuit of ventricular tachycardia (inset). Epicardial ablation (Panel B) requires the introduction of the catheter into the pericardial space by means of pericardial puncture; the black circular arrow shows a reentry circuit, and the red X indicates interruption by epicardial catheter ablation of the reentry circuit of ventricular tachycardia (inset). Target sites for catheter ablation can be identified with the use of three-dimensional electroanatomical voltage mapping (Panel C) to reconstruct regions of right ventricular scarring (i.e., either endocardial or epicardial low-voltage areas showing bipolar signal amplitude of <0.5 mV, indicated by red color coding), which represent the substrate for the reentry mechanism of ventricular tachycardia. The reentry circuit is interrupted by delivering radiofrequency energy through the ablation catheter to create point-by-point linear lesions (red circles), eliminating intrascar or interscar conducting pathways. The scale on the right shows the color coding of the electroanatomical map based on the myocardial signal amplitude, ranging from 0.03 mV (red) to 5.90 mV (magenta). On an electrophysiological recording obtained during catheter ablation (Panel D), ventricular tachycardia is interrupted abruptly after radiofrequency energy application (red arrow). Standard electrocardiographic leads I, III, V<sub>1</sub>, and V<sub>6</sub> are shown, as well as recordings from the ablation catheter itself at proximal (ABL p) and distal (ABL d) sites. LAD denotes left-axis deviation, LBBB left bundle-branch block, and RF radiofrequency.

death.<sup>65-68</sup> The poor long-term outcome has been attributed to the progressive nature of ARVC, which leads to the development of multiple arrhythmogenic foci over time. The epicardial location of some ventricular tachycardia reentry circuits, which reflects the propensity of ARVC lesions to originate and progress from the epicardium, may also explain the failure of conventional endocardial mapping and catheter ablation.<sup>1,4,66</sup> Several studies have shown the feasibility and efficacy of epicardial catheter ablation for patients in whom one or more endocardial procedures have been unsuccessful.<sup>66-70</sup>

Although randomized trials of defibrillator therapy have not been performed, data from observational studies have consistently shown



that it is effective and safe.<sup>37,58-62</sup> Patients who benefit most from defibrillators are those who have had an episode of ventricular fibrillation or sustained ventricular tachycardia. It remains uncertain whether defibrillator therapy is appropriate for primary prevention of sudden cardiac death among patients with one or more risk factors and no prior major arrhythmic events.<sup>52,57</sup> In asymptomatic patients with no risk factors and in healthy gene carriers, there is generally no indication for prophylactic defibrillator implantation because of the low risk of arrhythmias and the significant risk of device- and electrode-related complications during long-term follow-up (estimated rate, 3.7% per year).<sup>35-37,59,71</sup> It has become apparent that defibrillators may be inappropriately implanted in patients with a false diagnosis of ARVC based on misinterpretation of cardiac MRI studies.<sup>72,73</sup>

Patients in whom right or left heart failure develops are treated with standard pharmacologic therapy, including angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and diuretics.<sup>34,46,52</sup> Therapy with oral anticoagulants is reserved for patients with atrial fibrillation or thromboembolic complications. Cardiac transplantation is the ultimate therapy for patients with untreatable arrhythmias

(e.g., incessant storms of ventricular tachycardia or fibrillation) or congestive heart failure that is refractory to pharmacologic and nonpharmacologic therapies.<sup>74</sup>

Current therapeutic approaches to ARVC are palliative and partially alleviate symptoms and the risk of sudden cardiac death but do not prevent the development or progression of the disease process. A definitive curative treatment will require a deeper knowledge of the biologic mechanisms and environmental factors involved in the pathogenesis of ARVC. A recent observation concerns a small molecule designated SB216763, which is an activator of the Wnt signaling pathway. This molecule has been shown to prevent or reverse phenotypic manifestations of ARVC induced by overexpression of defective plakoglobin in a zebrafish model, as well as in rat cardiac myocytes.<sup>75</sup> Although this drug is of interest as a potential mechanism-based therapy of ARVC, it has not yet been studied in humans.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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