REVIEW ARTICLES

Arrhythmogenic Right Ventricular Cardiomyopathy

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Arrythmogenic right ventricular (RV) cardiomyopathy (ARVC) is a cardiomyopathy characterized pathologically by fibrofatty replacement primarily of the RV and clinically by life-threatening ventricular arrhythmias in apparently healthy young people. The prevalence of the disease has been estimated at 1 in 5,000 individuals, although this estimate will likely increase as awareness of the condition increases among physicians. Arrythmogenic RV cardiomyopathy is recognized as a cause of sudden death during athletic activity because of its association with ventricular arrhythmias that are provoked by exercise-induced catecholamine discharge. Diagnosis may be difficult because many of the electrocardiographic abnormalities mimic patterns seen in normal children, and the disease often involves only patchy areas of the RV. For this reason, international diagnostic criteria for ARVC were proposed by an expert consensus panel in 1996. Treatment is directed to preventing life-threatening cardiac arrhythmias with medications and the use of implantable defibrillators. This article will present in detail the etiology, clinical presentation, diagnosis and management of this condition. (J Am Coll Cardiol 2001;38:1773–81) © 2001 by the American College of Cardiology

Arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) is a myocardial disease affecting primarily the RV and characterized histologically by the gradual replacement of myocytes by adipose and fibrous tissue. Diagnostic criteria for ARVC were proposed in 1994 by an expert consensus panel (1,2).

Arrhythmogenic RV cardiomyopathy is an important cause of sudden death in individuals <30 years of age and has been found in up to 20% of sudden deaths in young people (2,3). Recently, there has been considerable interest in ARVC as a cause of sudden death in young athletes, and it is reported as the most common cause of exercise-related sudden death among young Italian athletes (2).

DEFINITION

The term "ARVC" was first proposed by Fontaine et al. (4) in a 1977 report describing six patients with sustained ventricular tachycardia (VT) who did not have overt heart disease and were resistant to antiarrhythmic drugs. Early reports have emphasized the localized RV involvement, but it is now clear that ARVC can progress to diffuse RV and left ventricular (LV) involvement and may culminate in biventricular heart failure (5,6). In this advanced stage, ARVC is difficult to distinguish clinically from dilated cardiomyopathy (7).

Genetics and family screening. The prevalence of ARVC in the general population is approximately 1 in 5,000 (8), but the disease is not widely recognized because of the difficulty in making the diagnosis (9). A familial predilection of the disease has been recognized since 1982 when Marcus et al. (10) described 24 cases of ARVC, two in the same family. Subsequently, several groups have reported familial ARVC, and families with two or more affected individuals have been recognized in Asian, Japanese, Northern European, African and North American populations (8).

The disease is typically inherited as an autosomal dominant trait with variable penetrance and incomplete expression. The genes responsible for ARVC have not been identified, but seven loci have been mapped to chromosomes 14 (14q23 to q24 and 14q12 to q22), 1 (1q42 to q43), 2 (2q32.1 to q32.2), 3 (3p23) and 10 (10p12 to p14) (2,11–13). The genetic products of these sites have not been easily identified because of incomplete penetrance and expression, age-related expression and difficulties with accurate diagnosis of the disease. Recently, plakoglobin has been identified as the first gene responsible for autosomal recessive ARVC (13). The gene was identified in Naxos disease where greater than 90% cosegregation of ARVC with cutaneous manifestations, woolly hair and keratodermia, facilitated case identification. Plakoglobin participates in forming cell-to-cell junctions. It is postulated that inadequate cell adherence damages the cardiac cell membranes leading to cell death and fibrofatty replacement.

The cardiac ryanodine receptor gene (RyR2) has also recently been implicated in ARVC (14) and offers potential insight into the association of adrenergically mediated ventricular arrhythmias with this disease. The ryanodine receptor induces calcium release from the sarcoplasmic reticulum into the cytosol (14). The cardiac ryanodine receptor has also been identified as being responsible for catecholamine-induced ventricular tachycardia (15,16). Its skeletal muscle counterpart has been implicated in malig-

Abbreviations and Acronyms

ARVC = arrhythmogenic right ventricular cardiomyopathy
CHF = congestive heart failure
CT = computerized tomography
ECG = electrocardiogram
ICD = implantable cardioverter defibrillator
LV = left ventricle or left ventricular
MRI = magnetic resonance imaging
NSVT = nonsustained ventricular tachycardia
PVC = premature ventricular complex
RBBB = right bundle branch block
RV = right ventricle or right ventricular
RVOT = right ventricular outflow tachycardia
VT = ventricular tachycardia

nant hyperthermia and central core disease (17), a congenital myopathy, but the mechanisms by which mutations in the cardiac ryanodine receptor might mediate fibrofatty myocardial changes are not clear and will likely be the focus of future studies. Despite these advances, genetic analysis for ARVD is not clinically available and is restricted to research laboratories.

Histopathology. Characteristically, the RV in ARVC is replaced with a fibrofatty tissue. Morphologic alterations of ARVC usually begin in the subepicardium or mediomural layers (8,18) of the RV and progress to the endocardium with fibrofatty replacement of myocytes and thinning of the wall. The regions of RV most frequently involved are the RV inflow area, the apex and the infundibulum. These three areas form "the triangle of dysplasia" (2,19). However, small amounts of fat are present in the epicardial layer and within the RV myocardium in normal subjects. Fontaine et al. (20) examined the hearts at necropsy in 140 individuals with no history of heart disorders. Over 50% of the subjects had fat within their RV myocardial fibers, and the presence of intramyocardial fat increased with age. Therefore, histologic diagnosis of ARVC may be difficult in borderline cases. To avoid overdiagnosing ARVC, Angeline et al. (21) have proposed that the presence in biopsy sections of more than 3% of fibrous tissue and more than 40% of fatty tissue is highly suggestive of ARVC. These authors also emphasized the importance of identifying coexisting myocardial fibrosis in making the diagnosis. In a forensic autopsy study of 20 patients with ARVC who died suddenly (22), the fatty replacement involved the outer half of RV free wall in 27%, the outer two-thirds in 28% and the entire wall thickness in 45% of the cases. Interestingly, the endocardial muscular trabeculae are generally spared but may occasionally also be atrophied (22,23). The LV was involved in 40% of cases in this report (22), although other reports have identified LV involvement in up to 76% of individuals with ARVC examined at necropsy (6). When the LV is involved, the fibrofatty replacement can affect both the septum and LV free wall, either diffusely or, more often, regionally with a predilection for the posteroseptal and posterolateral areas.

In the LV, fatty replacement of the myocardium has a predilection for the subepicardial and midventricular wall (6).

ETIOLOGY

In addition to a genetic cause of ARVC, disontogenetic (19,23), degenerative (23,24), infectious or inflammatory (25–28), apoptotic (29,30) and myocyte transdifferentiation (31) theories have been proposed either as the cause of or as environmental factors facilitating gene expression.

The disontogenetic theory is largely historical but suggests that ARVC is a milder form of "parchment RV" or Uhl's anomaly (19,23), a congenital hypoplasia of the RV myocardium, which presents in infancy as congestive heart failure (CHF) (32).

The degenerative theory suggests that ARVC is a consequence of myocyte death due to an inherited metabolic or ultrastructural defect. A possible defect has been mapped to chromosome l4q23 to q24 (33). This area encodes for the alpha actinin gene, which shares structural homology with the amino terminal domain of dystrophin. This finding supports the concept of a genetically determined atrophy similar to that in patients with Duchenne's or Becker's muscular dystrophy. Some have suggested that ARVC should be considered as a "myocardial dystrophy" (23). Furthermore, skeletal muscle involvement has been reported in a Swedish family with ARVC, and the defect has been tentatively localized to chromosome 10q22.3 (34).

The infectious or inflammatory theory maintains that the disease results from previous myocarditis. Inflammatory infiltrates are common in histologic specimens from patients with ARVC. Fontaine et al. (25) found inflammatory infiltrates in 8 of 27 patients with ARVC. BALB/C mice infected with Coxsackie virus B_3 develop selective RV myocardial cell death, acute mononuclear cell infiltration and subsequent RV aneurysm formation (27). Furthermore, enteroviral RNA with homology to Coxsackie viruses type B has been detected in three of eight patients with ARVC and in 7 of 23 patients with myocarditis or dilated cardiomyopathy (28).

An apoptotic theory is supported by the finding of apoptosis and a high level of CPP-32, a cysteine protease required for apoptosis, which were detected in the RV myocardium of six of eight patients with ARVC but not in four normal subjects (29,30).

The transdifferentiation theory is based on the hypothesis that myocardial cells can change from muscle to adipose tissue and the observation in one patient that "transitional cells" at the interface between cardiac muscle and adipose tissue expressed both desmin, which is characteristic of muscle tissue, and vimentin, expressed only in adipocytes (31).

CLINICAL PRESENTATION

Arrhythmogenic RV cardiomyopathy typically occurs in young adult men. At least 80% of cases are diagnosed before

the age 40. Arrhythmogenic RV cardiomyopathy should be considered in young patients presenting with syncope, VT, cardiac arrest or in adult patients with CHF (35).

Arrhythmia. The VT in patients with ARVC usually has a left bundle branch block morphology, reflecting origin of the arrhythmia from the RV. Some patients have multiple VT morphologies because the disease can produce multiple arrhythmogenic foci. Many relatives of ARVC probands have a history of syncope that is undiagnosed, in part because they lack other features suggestive of ARVC. This has been labeled "concealed ARVC" (2,36). Many of these cases subsequently develop progressive electrocardiogram (ECG) changes typical of ARVC and are then labeled as "revealed ARVC" (8).

Sudden death. In the U.S., ARVC accounts for approximately 5% of sudden cardiac deaths in individuals under the age of 65 (37) and is responsible for at least 3% to 4% of deaths associated with physical activity in young athletes (38). In the Veneto region of Italy, ARVC is the most common cause of sudden arrhythmic deaths in individuals under the age of 35 years and the overwhelming cause of sudden death associated with exertion in young athletes in Italy (12,26,39). The annual mortality rate of ARVC has been estimated at 3% without treatment and at 1% with pharmacologic medical treatment not including implanted automatic defibrillators (40). The mechanism of sudden death in ARVC is, in most cases, acceleration of VT with degeneration into ventricular fibrillation.

Peters et al. (41) sought to identify patients with ARVC who were at greatest risk of cardiac arrest. They analyzed angiographic and electrophysiologic data from 60 patients with documented ARVC. Twenty had spontaneous non-sustained VT (NSVT); 27 had sustained VT, and 13 suffered cardiac arrest with documented ventricular fibrillation. Global RV function was reduced in patients with cardiac arrest, and the reduction was most pronounced in those cases with cardiac arrest and inducible ventricular arrhythmia. Hypokinetic segments as well as end-diastolic and end-systolic bulges were also more frequent in patients who had suffered a cardiac arrest and had an inducible ventricular arrhythmia. Approximately 40% of the patients had LV wall motion abnormalities despite normal global LV function (mean LV ejection fraction 60 ± 11%). These patients did not have an increased incidence of spontaneous ventricular arrhythmia. The authors concluded that functional and structural worsening of RV performance was the major risk factor for cardiac arrest in patients with ARVC.

Triggering events and mechanisms of arrhythmias. The islands of fibrofatty tissue found in ARVC generate macro reentry electrical circuits and form the arrhythmogenic substrate for the malignant cardiac arrhythmias responsible for sudden death in these patients. These arrhythmias are typically induced by adrenergic stimulation such as catecholamine infusion or physical exercise (42). Most patients with ARVC are susceptible to adrenergic stimulation, and 80% develop either ventricular extrasystoles or VT during iso-

prenaline infusion (43). Additional evidence supports the concept that VT in ARVC is due to sympathetic stimulation. Ambulatory ECG recordings of patients developing sustained VT demonstrate a progressive increase in the sinus rate before the onset of the arrhythmia, suggesting progressive sympathetic stimulation (43). Ventricular tachycardia in ARVC is characteristically monomorphic and rarely initiated by complexes of a different configuration, suggesting that the arrhythmia originates from a single focus. This contrasts with the monomorphic VT observed in patients with coronary artery disease, which is often initiated by premature ventricular complexes (PVC) from a different focus. The role of sympathetic stimulation in provoking arrhythmias in ARVC probably accounts for the high prevalence of this condition in individuals who die during exertion.

Heart failure. Patients with ARVC may develop isolated right heart failure or biventricular failure. This presentation of ARVC typically appears in the fourth and fifth decades of life (8). Arrhythmogenic RV cardiomyopathy is one of the few myocardial diseases that causes RV heart failure without pulmonary hypertension. The mechanism for the RV failure is dilation, thinning of the wall and progressive loss of contractile function because of myocardial atrophy. Right heart failure typically presents in ARVC four to eight years after the appearance of complete right bundle branch block (RBBB) on the ECG (37). Arrhythmogenic RV cardiomyopathy can involve the LV and produce mild decreases of LV function, although left-sided heart failure is unusual. When left heart failure does occur, it may be misdiagnosed as idiopathic or viral dilated cardiomyopathy (8). Left-sided dysfunction in ARVC may represent "biventricular dysplasia" and must be differentiated from biventricular myocarditis with fibrosis (27). Making the correct diagnosis is important since patients with ARVC tend to be more susceptible to drug-resistant arrhythmia and sudden death and may require other treatment options such as an automatic implantable cardioverter defibrillator (ICD) or cardiac transplantation. Clinicians should consider the possibility of ARVC if the patient has an apparent dilated cardiomyopathy with a resting ECG showing right precordial T-wave changes.

DIAGNOSIS

A definite diagnosis of ARVC requires the histologic finding of transmural fibrofatty replacement of RV myocardium at necropsy (Fig. 1), surgery or endomyocardial biopsy (Fig. 2). Diagnosis by endomyocardial biopsy is difficult, however, because the disease is segmental and because the interventricular septum, the area usually biopsied, is rarely involved (1). Because of the difficulty in establishing a diagnosis, an expert consensus group has proposed criteria for the diagnosis (Table 1). To qualify as ARVC, a patient must demonstrate either two major criteria, one major criteria plus two minor criteria or four minor criteria (1).
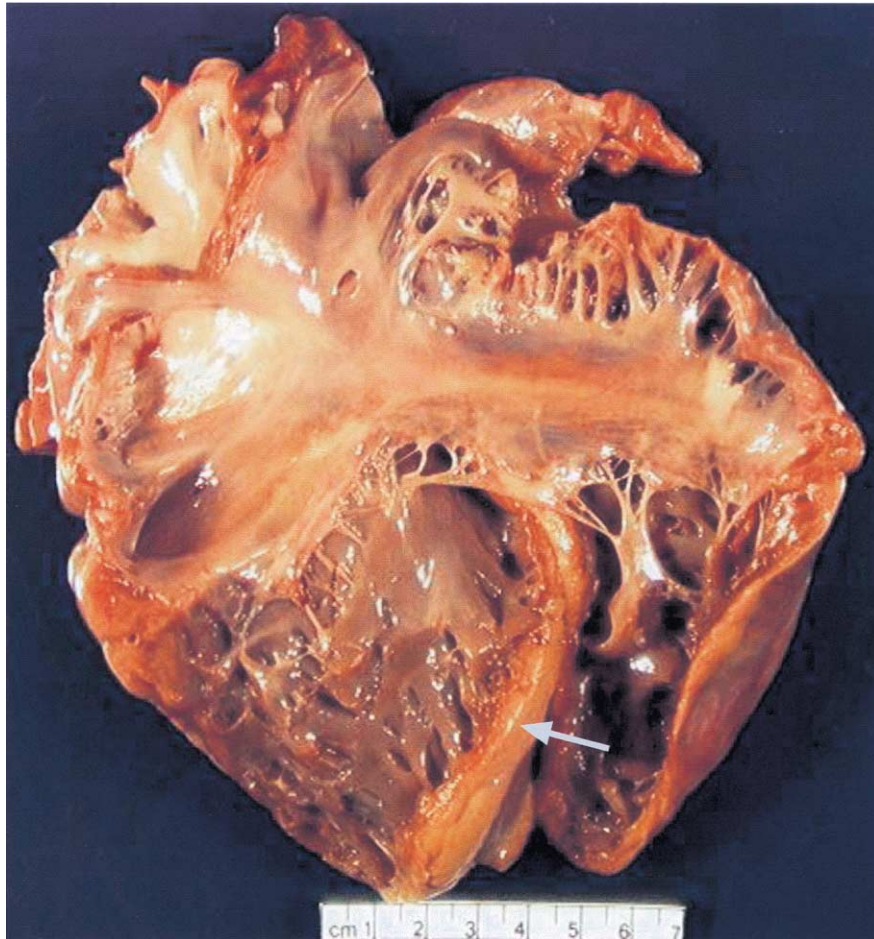
Figure 1. Heart of a 37-year-old woman admitted with heart failure who suffered a subsequent cardiac arrest. The **arrow** identifies fatty infiltration of the right ventricle.

ECG findings. Repolarization abnormalities manifested by T-wave inversion in leads V_1 to V_3 in the absence of a complete RBBB are a minor diagnostic criterion but are extremely useful in raising the suspicion of ARVC and are present in up to 54% of cases (18) (Fig. 3). This finding is
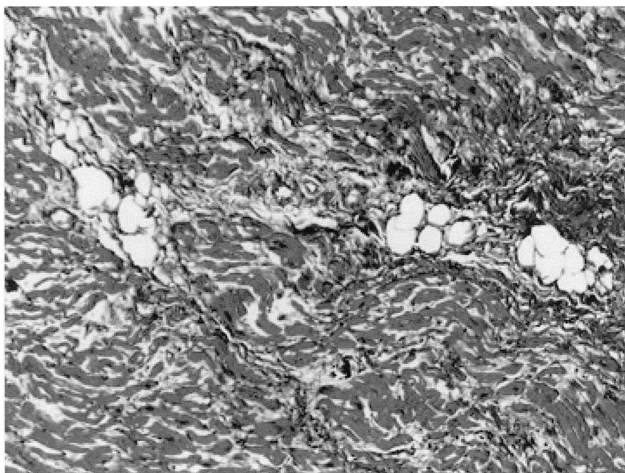

Figure 2. Trichrome-stained section from the right ventricle of the patient from Figure 1 showing increasing fibrous and adipose tissue throughout the ventricular wall ($\times$200).

difficult to differentiate from normal findings, however, because many children and young subjects have T-wave inversions in the right precordial leads, and this is consequently a diagnostic criterion only in individuals >12 years old (44). Furthermore, young, trained athletes also may demonstrate ECG patterns consistent with ARVC in the absence of pathologic cardiac conditions (45). The presence of marked T-wave inversions in all precordial leads correlates with LV involvement (18) and, in patients with ventricular arrhythmias, indicates a high risk of recurrence.

Some patients demonstrate signs of depolarization delay such as RBBB or incomplete RBBB, although these patterns alone are not criteria for the diagnosis because they can be found not uncommonly in healthy subjects. Complete RBBB is found in approximately 15% of patients with ARVC, and incomplete RBBB is observed in 18% (18). Along with the conduction delay, there may also be low voltage in the rapid phase of the QRS related to the loss of RV myocardium. Selective prolongation of the QRS in leads V_1 to V_3 compared with lead V_6 is an additional major criterion and is satisfied if the QRS duration in leads V_1 to V_3 is 50 ms above the QRS duration in lead V_6 in the presence of RBBB (46).

Table 1. Criteria for Diagnosis of RV Dysplasia

I. Global or regional dysfunction and structural alterations*
MAJOR
Severe dilation and reduction of RV ejection fraction with no (or only mild) LV impairment.
Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging).
Severe segmental dilation of the RV.
MINOR
Mild global RV dilation or ejection fraction reduction with normal LV.
Mild segmental dilation of the RV.
Regional RV hypokinesia.
II. Tissue characterization of walls
MAJOR
Fibrofatty replacement of myocardium on endomyocardial biopsy.
III. Repolarization abnormalities
MINOR
Inverted T waves in right precordial leads (V_2 and V_3) (people aged more than 12 yr; in absence of right bundle branch block).
IV. Depolarization/conduction abnormalities
MAJOR
Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3).
MINOR
Late potentials (signal-averaged ECG).
V. Arrhythmia
MINOR
Left bundle branch block type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise testing).
Frequent ventricular extrasystoles (more than 1,000/24 h) (Holter).
VI. Family history
MAJOR
Familial disease confirmed at necropsy or surgery.
MINOR
Familial history of premature sudden death (<35 yr) due to suspected RV dysplasia.
Familial history (clinical diagnosis based on present criteria).

*Detected by echocardiography, angiography, magnetic resonance imaging or radionuclide scintigraphy
ECG = electrocardiogram; LV = left ventricle or left ventricular; RV = right ventricle or right ventricular.

Epsilon waves are a major diagnostic criterion that are found in up to 30% of cases of ARVC (5,18). Epsilon waves are "postexcitation" electrical potentials of small amplitude
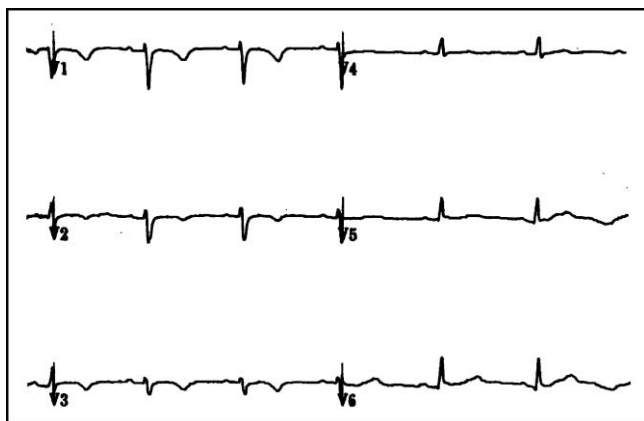

Figure 3. Electrocardiogram of a 32-year-old woman with arrhythmogenic right ventricular cardiomyopathy showing right precordial T-wave inversions.

that occur at the end of the QRS complex and at the beginning of the ST segment (Fig. 4). They are highly specific for ARVC and reflect delayed RV activation. Peters et al. (27) found that maximum QRS duration in right precordial leads of ≥110 ms and left precordial JT interval prolongation characterized quantitatively by a JT interval dispersion of ≥30 ms represented a noninvasive predictor of recurrent arrhythmic events. The presence of RBBB on ECG with QRS precordial dispersion ≥50 ms generally characterized patients with massive RV dilation and recurrent episodes of VT or ventricular fibrillation.

Signal-averaged ECG. Late action potentials on signal-averaged ECG recordings are a minor criterion for the diagnosis of ARVC. Late action potentials on the signal-averaged ECG are the counterpart of the epsilon waves recorded on the surface ECG. Consistent with other ECG abnormalities in ARVC, the abnormalities on signal-averaged ECG are more prominent in the right precordial leads than they are in the left precordial leads (5).

Between 50% to 80% of patients with ARVC and clinical VT have an abnormal signal-averaged ECG (47,48). The signal-averaged ECG may be normal if the disease is localized to a small segment of the RV, but such patients are not immune to malignant arrhythmias. Abnormal signal-averaged ECG recordings are more common in patients with more severe myocardial fibrosis and reduced RV ejection fraction and predict sustained VT among ARVC patients with prior nonsustained VT (47).

Echocardiographic findings. Echocardiography can be used to evaluate RV and LV size and function, which are important major and minor criteria for the diagnosis of ARVC. The most prevalent finding is a severely hypokinetic and dilated RV, although the spectrum of abnormalities may range from a normal RV to severe RV dilation and hypokinesis (49). Generally, the structural abnormalities in ARVC are moderate and easily overlooked. The most suggestive echocardiographic findings for ARVC include dilation of the RV, with localized aneurysms during diastole and dyskinesis in the inferior basal region (18). The RV function should be measured at several points including the RV inflow tract, body and outflow tract regions because of the focal nature of the disease (50). The most important other echocardiographic parameters in establishing the diagnosis are the RV end-diastolic and end-systolic diameters, as well as the ratio of the RV to LV end-diastolic diameters. A ratio of >0.5 for the RV/LV end-diastolic diameter has a sensitivity of 86%, a specificity of 93% and a positive predictive value of 86% for the diagnosis of ARVC (5).

The negative predictive value is 93%, making this parameter an extremely useful diagnostic measurement. More extreme RV compared with LV dilation is even more suggestive of ARVC. Manyari et al. (51) found that all of 14 patients with RV cardiomyopathy had an RV/LV end-diastolic volume ratio >1.8 or an exercise RV ejection fraction <50%. Subtle findings include localized abnormalities of right heart cavity such as increased reflectivity of the
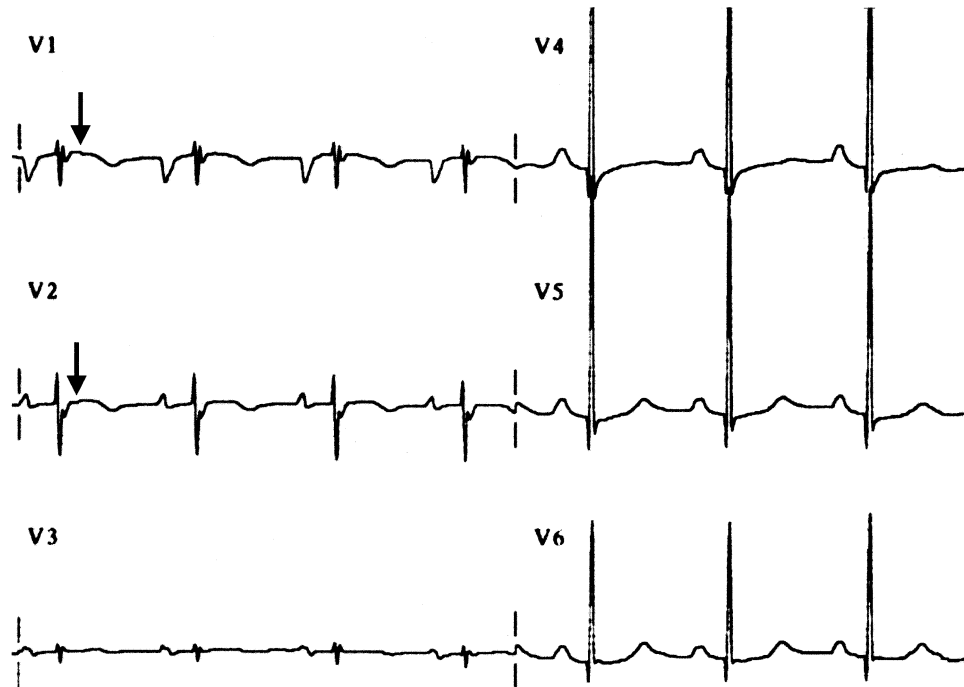
Figure 4. Electrocardiogram (ECG) of an 18-year-old male patient diagnosed with arrhythmogenic right ventricular cardiomyopathy by cardiac angiography and refractory ventricular tachycardia requiring a defibrillator. The ECG is magnified to demonstrate the epsilon waves **(arrow).** The QRS duration is greater in the right ventricular leads than it is in V$_6$. The ECG also shows biatrial enlargement.

moderator band and prominent trabeculations of the RV apex (18).

RV angiography. Right ventricular angiography is still considered by many experts the method of choice for evaluating RV function (5,18). The RV is best evaluated by biplane angiography with views obtained in the 45° right anterior oblique and 45° left anterior oblique to assess the areas commonly involved in ARVC such as the infundibulum, the anterior RV free wall and inferior wall, especially the subtricuspid area (2,18). The RV angiogram should be obtained during sinus rhythms without frequent PVCs. Potential abnormal findings on RV angiography include (18): infundibular aneurysms, trabeculae thicker than 4 mm that give the appearance of "deep fissures," a prominent moderator band, apical aneurysms, multiple out pouchings of the inferior wall, diastolic bulging of the subtricuspid area and, in severe cases, tricuspid valve prolapse, usually associated with mild tricuspid insufficiency. The coexistence of subtricuspid and anterior infundibular wall bulging as well as hypertrophic trabeculae is associated with 96% specificity and 87.5% sensitivity for the diagnosis of ARVC (2,5).

Computerized tomography (CT) and magnetic resonance imaging (MRI). Computerized tomography and MRI have recently been added to the techniques used to diagnose ARVC. Compared with conventional CT, electron-beam CT provides superior temporal resolution and enables better evaluation of the ventricle because of its ability to acquire motionless cardiac and cross-sectional images. Characteristic findings of ARVC on electron-beam CT findings include abundant epicardial adipose tissue,

prominent trabeculations with low attenuation, a scalloped appearance of the RV free wall and intramyocardial fat deposits (9).

Magnetic resonance imaging is a potentially useful test because it can distinguish fat from muscle. Cine MRI also provides good contrast between the blood pool and the myocardial wall and, therefore, can provide information about RV wall motion and function (2,52). However, there are some limitations to this technique. The RV free wall is thin, resulting in insufficient spectral resolution to adequately quantify the RV thickness, in addition to the normal presence of epicardial and pericardial fat causing difficulty in identifying intramyocardial fat (2,12).

MANAGEMENT OF PATIENTS WITH ARVC

Pharmacologic therapy. There are few studies evaluating treatment strategies in asymptomatic patients with mild morphologic RV alterations and no evidence of arrhythmia. Beta-adrenergic blocking agents are a reasonable recommendation in these patients to reduce the possibility of adrenergically stimulated arrhythmia. In the presence of arrhythmia (NSVT, VT or frequent and complex PVCs) or symptoms, treatment should be initiated with beta-blockers or ICD with additional medical therapy to prevent defibrillator discharge.

Wichter et al. (42) evaluated the effectiveness of sotalol in 81 patients who had either ARVC or RV outflow tachycardia (RVOT). Sotalol prevented VT during programmed ventricular stimulation in 68% of the patients, whereas class

I_a and I_b drugs were effective in only 5.6% and class I_c drugs in only 2% of patients. Patients unresponsive to sotalol were unlikely to respond to amiodorone when evaluated by programmed ventricular stimulation (5). In patients in whom VT could not be induced during programmed ventricular stimulation, efficacy was determined by suppression of ventricular arrhythmias during Holter monitoring and exercise testing. Sotalol was again the most effective drug, with 83% of patients responding. Verapamil was the next most effective. No patients appeared to be responsive to class I_a or I_b drugs, and only 17% responded to class I_c drugs. Unfortunately, 10% of the patients had a repeated episode of nonfatal VT during a follow-up period of 34 months, which raises the question as to whether even the best antiarrhythmic agents are effective for long-term treatment of symptomatic patients. In addition, other limitations should be considered. It was not specified how many patients had ARVC and how many had RVOT; the prognosis in these two conditions are different, with ARVC being much more life-threatening. The assignment of patients to various antiarrhythmic therapies was not random. Nevertheless, this study remains the largest examination in patients with RV tachycardia and provides some guidance for the use of sotalol.

Amiodarone has both mild beta-blocking effects and antiarrhythmic characteristics and has been effectively used either alone or in combination with other agents to prevent recurrent cardiac arrhythmia, but no studies have addressed the use of amiodarone in this patient group (5).

Radiofrequency ablation. Radiofrequency ablation of an arrhythmogenic focus can be attempted in patients who are unresponsive or intolerant to antiarrhythmic drugs but is frequently unsuccessful and may require multiple attempts. Fontaine et al. (53) reported success rates of 32%, 45% and 66% after one, two or three ablation sessions in 50 patients, most of whom had not had success with other therapy and were followed for a mean of 5.4 years after ablation. Ablation may be unsuccessful because of the progressive nature of the disease and the diffuse, yet patchy, nature of the disease, which produces multiple arrhythmogenic foci. Consequently, ablation of one focus may unmask other arrhythmogenic areas (5).

ICD. Patients who are considered to be at high risk for sudden cardiac death should receive an ICD. This includes patients who have been resuscitated from cardiac arrest, with history of syncope or who have threatening arrhythmias that are not completely suppressed by antiarrhythmic drug therapy. The risk of sudden death in such patients is increased and should prompt consideration of ICD implantation.

Nevertheless, this approach does not imply that there are no risks to the implantation in patients with ARVC. First, areas of the RV myocardium in patients with ARVC are thin and noncontractile and can be penetrated during placement of the RV leads with subsequent tamponade. Second, the fibrofatty nature of the RV may lead to

difficulty in the device adequately sensing arrhythmias with improper ICD function or failure (54).

Sudden death in competitive athletes with ARVC. Arrhythmogenic RV cardiomyopathy has been recognized as an important cause of sudden death in association with exercise and athletic participation. Its frequency as a cause of such exercise-related events in some reports is related to its prevalence, its predilection to produce malignant ventricular arrhythmias in young subjects and the fact that these arrhythmias are often provoked by adrenergic stimulation.

Furlanello et al. (55) examined 1,642 competitive athletes referred for cardiac arrhythmia detected as part of a national preparticipation athletic screening program in Italy. A total of 6% were diagnosed with ARVC using World Health Organization criteria. These athletes were followed for an average of eight years, and 4% of them suffered either a cardiac arrest or sudden death. Individuals with ARVC comprised 23% and 25% of all athletes suffering either a cardiac arrest or sudden death, confirming that ARVC is the dominant cause of exercise-related sudden death among Italian athletes. All cardiac arrests in athletes with ARVC occurred during athletic activity, supporting the importance of exercise-induced adrenergic stimulation in provoking malignant arrhythmias in these patients. More than 60% of the patients with ARVC had important prodromal symptoms such as syncope before their collapse; these prodromal symptoms were also related to athletic activity but did not lead to a premortem diagnosis and appropriate treatment.

Because of the risk of sudden death in patients with ARVC, young subjects with this condition should be prohibited from vigorous athletic competition (56). This prohibition remains in effect even after the subjects have received effective treatment such as in ICD placement because athletic competition may induce incessant ventricular fibrillation that cannot be terminated, given the response patterns of present devices. Specifically, most devices are programmed to deliver a total of six shocks. If the arrhythmia persists, additional shocks will not be delivered without an interval period of sinus rhythm to prevent recurrent shocking of an artifact pattern.

Conclusions. Arrhythmogenic RV cardiomyopathy is increasingly recognized as a cause of malignant ventricular arrhythmias among apparently healthy young subjects and individuals engaged in vigorous exercise. Physicians should consider this condition in young subjects with cardiac arrhythmias or unexplained cardiomyopathy. Management involves the suppression of malignant arrhythmias with various pharmacologic agents but is increasingly directed toward placement of automatic implantable defibrillators as the most effective treatment to prevent sudden cardiac death.

ECGs in Figures 3 and 4. The authors would also like to thank William McKenna, MD, for his thoughtful comments on the manuscript.

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