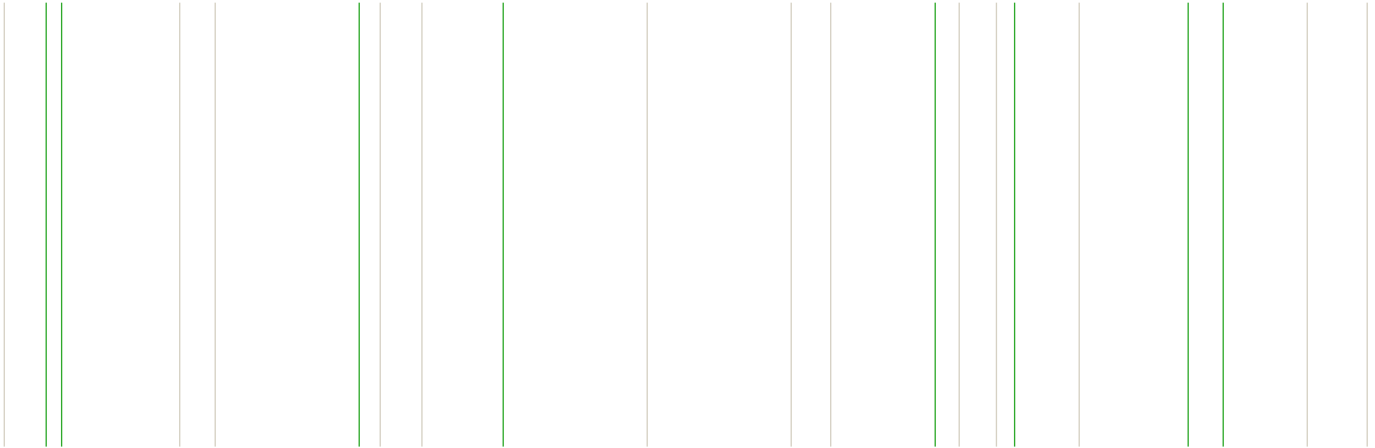


A clinical profile of ARVD was described 20 years ago, yet there are still many unanswered questions about the natural history of this condition.



What Is ARVD?

Drs. Frank Marcus and Guy Fontaine first described the clinical features of arrhythmogenic right ventricular dysplasia (ARVD) in 1982. ARVD is an important cause of sudden death among young athletes in their 20s and 30s, although people within a broad range of ages and activity levels have this condition. It affects men and women of all races, and the incidence is estimated to be as high as 1 in 5,000 people.

2 A team from Johns Hopkins and the University of Arizona wrote this brochure to provide physicians with information about the diagnosis, treatment, and genetics of ARVD and to introduce the NIH-funded Multidisciplinary Study of Right Ventricular Dysplasia. This brochure also contains a brief review of the practical considerations concerning the diagnosis and management of ARVD.

As with any rare condition, the severe and unusual cases are overrepresented in the medical literature. Unfortunately, there are few long-term follow-up studies of large numbers of patients, making it difficult to answer many questions that physicians and patients pose. The Multidisciplinary Study of Right Ventricular Dysplasia will enable physicians

to collaborate and study large numbers of patients to learn more about the diagnosis and treatment of this condition. We hope that you find this brochure useful in caring for your patients and in referring them for the Multidisciplinary Study of Right Ventricular Dysplasia.

Who Should Be Evaluated for ARVD?

ARVD usually comes to clinical attention because of ventricular arrhythmias (VAs) that originate in the right ventricle. These VAs range from isolated premature beats to sustained ventricular tachycardia (VT) or ventricular fibrillation. Some VAs may be asymptomatic and detected only by a routine ECG, or they may cause palpitations, syncope, or sudden cardiac death. Patients with ARVD usually present with VAs after puberty and before age 45, and there is a predominance of male patients. Exercise is a common precipitant of the arrhythmia in patients with ARVD, as well as in those with the more common idiopathic VT that arises from the right ventricular outflow tract.

Idiopathic VT frequently arises from the right ventricular outflow tract. It is similar to ARVD because it (1) occurs with exercise; (2) has a left bundle branch block morphology; and (3) occurs predominantly in young, otherwise healthy people. The absence of structural heart disease and other ECG abnormalities helps to distinguish idiopathic VT from ARVD. In fact, all patients being evaluated for idiopathic VT or unexplained sudden death should be screened for ARVD.

Patients with ARVD can also present with right ventricular enlargement detected by echocardiography or a chest X-ray. Other entities to be considered in patients with right ventricular enlargement include atrial septal defect, anomalous pulmonary venous return, and Ebstein's malformation. In later stages of ARVD, patients can develop left ventricular dilation, which resembles dilated cardiomyopathy. Even when ARVD is suspected, there is no single test to establish or exclude the diagnosis of ARVD.

Other ARVD Symptoms and Pathologic Findings

The following additional information alerts physicians to suspect a diagnosis of ARVD.

Symptoms. A minority of patients with ARVD develop atrial arrhythmias, usually late in the disease course. In most cases, the atrial arrhythmias can be treated medically.

The VT found in patients with ARVD is usually re-entrant, and multiple re-entrant circuits may be present. The three most commonly affected regions of the right ventricle, sometimes referred to as the triangle of dysplasia, are the anterior surface of the pulmonary infundibulum, the apex, and the subtricuspid region. These regions also correspond to the locations of wall motion abnormalities, aneurysms, and bulges seen on echocardiograms, right ventricular angiograms, and magnetic resonance cine images.

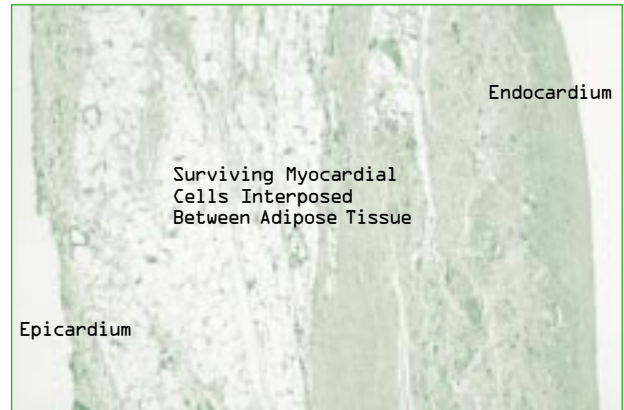
There are currently no known extra-cardiac signs of ARVD. The exception is Naxos disease, which is an autosomal recessive condition found in patients on the island of Naxos in Greece. Naxos disease is a combination of right ventricular dysplasia, palmoplantar hyperkeratosis, and woolly hair. These ectodermal signs that are present within

the first years of life clearly differentiate patients with Naxos disease from those with ARVD. It is exceedingly rare to find Naxos disease in patients from other regions of the world, although a few cases have been reported in other countries.

Pathology. At autopsy, ARVD exhibits segmental or diffuse replacement of the right ventricular myocardium with fatty and fibrofatty tissue. The myocardium can be thinned and atrophic, or thickened with infiltrative fatty and fibrofatty tissue. These morphologic findings are difficult to ascertain with echocardiography or magnetic resonance imaging (MRI). Fatty tissue replacement is most severe in the areas near the epicardium and mid-myocardium. Typically, the right ventricular free wall is affected first. The disease may progress to the left ventricle. Abnormalities of the right and left atrium have not been well studied. Evidence for both acute and chronic myocarditis has been seen in some cases, but most endomyocardial biopsies from ARVD patients show only mild signs of inflammatory cell infiltrates.

It is important to note that adipose tissue is normally found on the epicardial surface of the heart and in some areas of the conduction system. However, this epicardial fatty tissue is distinctly different in its distribution from the infiltrative fatty and fibrofatty tissue seen in ARVD.

There are three proposed theories for explaining how the fatty and fibrofatty tissue form in these patients. One theory is that because of apoptosis, the myocytes die prematurely, and fatty and fibrofatty tissue replace them. The second is that for some unknown reason, the myocytes transdifferentiate into fatty and fibrofatty tissue. The third is that inflammation, such as that caused by a viral myocarditis, destroys the myocytes, and during the healing process, fatty and fibrofatty scars replace the myocytes. There is some scientific evidence for all of these theories, but many questions remain unanswered.



Histologic specimen from the right ventricular free wall of a patient with ARVD. Surviving myocardial cells are interposed between adipose tissue. The endocardium is usually spared.

Genetics. ARVD is genetic and inherited as an autosomal dominant condition. Severity varies from person to person, even within the same family. An affected individual has a 50% risk of passing the gene for ARVD to his or her child. It is estimated that half of the patients have a family history of ARVD; the remaining cases are new mutations (i.e., the first person in the family to be affected).

The physician may uncover the presence of a family history after careful questioning about the ages and causes of death in the extended family, paying careful attention to premature sudden deaths. A review of autopsy reports can provide valuable information to substantiate the diagnosis of ARVD and impact the screening of other family members. Referral to a genetic counselor can help to determine the risks to family members for ARVD and other conditions that may be present in the family.

Linkage analysis has identified six genetic loci (positions) on chromosomes 1, 2, 3, 10, and 14 for the autosomal dominant form of ARVD. Some families are not linked to these loci, which suggests further genetic heterogeneity (i.e., more genes not found thus far). Evidence indicates

that there may be different phenotypic expressions of the different genes. There are both intrafamilial and interfamilial variations in disease presentation and severity. Thus, first-degree relatives (parents, siblings, and children above the age of puberty) should be screened for ARVD, with follow-up screenings every 3 to 5 years, as signs and symptoms may have a later onset.

Mutations in the cardiac ryanodine receptor gene (RYR2) on chromosome 1 were reported in several Italian families with ARVD and effort-induced polymorphic VT. These families appear to be clinically distinct from other patients with ARVD in four ways: (1) the type of tachycardia (polymorphic), (2) the limitation of pathology to the right ventricular apex, (3) the high penetrance rate, and (4) the equal numbers of males and females affected. Genetic testing for RYR2 mutations is not currently available on a clinical basis. The gene for Naxos disease was identified in 2000 as plakoglobin, when 19 patients exhibited a homozygous mutation causing a frameshift. Patients with the autosomal dominant form of ARVD did not have mutations in plakoglobin when tested, providing more evidence of the disease's significant heterogeneity.

The Diagnostic Evaluation of ARVD

The diagnosis of ARVD is based on the findings of electrical, anatomical, and functional abnormalities that predominantly affect the right ventricle.

Non-Invasive Testing. Patients suspected of having ARVD should have a non-invasive cardiac evaluation, including electrocardiography, signal-averaged electrocardiography, an exercise stress test, echocardiography, and a 24-hour Holter monitor. Refer to page 14 for the typical ECG findings. Although echocardiography is widely available, it is unusual to focus on the morphology of the right ventricle. Therefore, specific protocols performed by technicians trained in this approach help to yield optimum information.

It has been proposed that MRI may be the single best test to diagnose ARVD. However, the role of MRI in the evaluation of patients with ARVD is extremely controversial. It is now well recognized that a diagnosis of ARVD should not be based solely on MRI results. There are wide-ranging MRI techniques and equipment, and no standard MRI protocol exists for the right ventricle. Although MRI is widely available, most centers do not perform MRIs of the right ventricle on a routine basis. Optimal MRI scans of the right ventricle

require specific imaging protocols, state-of-the-art imaging equipment, and experienced radiologists.

Invasive Testing. If the non-invasive cardiac testing is abnormal, then the patient should undergo the following three invasive tests to confirm the diagnosis and guide treatment: (1) right ventriculography, (2) electrophysiology (EP) testing, and (3) endomyocardial biopsy.

Right ventriculography is key among clinicians experienced in diagnosing ARVD. The detection of bulges, aneurysms, and other wall motion abnormalities on an angiogram can provide important diagnostic information. A standard protocol for ventriculography is available, and the EP test can be done concurrently. The EP test should include programmed electric stimulation in two locations of the right ventricle, with and without an infusion of isoproterenol. Re-entrant VT and multiple foci of VT are common findings in patients with ARVD.

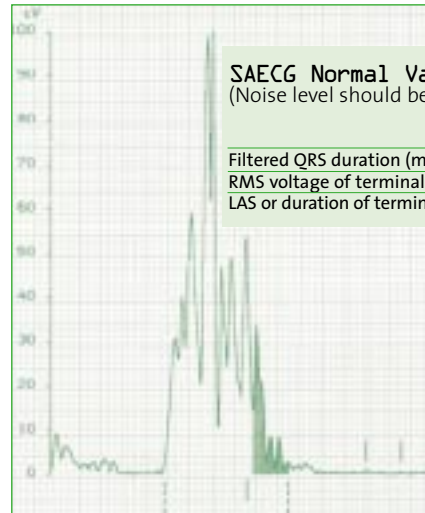
An endomyocardial biopsy of the ventricular septum is not optimal for diagnosis of this disease since ARVD does not usually involve this region of the heart. Because

ARVD can be segmental, a normal biopsy does not negate the diagnosis of ARVD. Only specialists who are trained in the proper techniques should take biopsies of other regions of the right ventricle, such as the free wall. When the biopsy from an affected region of the right ventricle has been analyzed histologically and the amount of fatty and fibrofatty tissue has been quantified, there is a high specificity for the diagnosis.

Diagnostic Criteria. A physician analyzes information from the physical exam, family history, and cardiac testing to determine whether it conforms to proposed major and minor criteria for ARVD that have been published by a task force. However, since these criteria have not been prospectively validated, there is some concern that they may lack sensitivity at the expense of being very specific. Diagnosing ARVD in its early stages or in patients with a positive family history is particularly challenging.

Once a patient is diagnosed with ARVD, all first-degree relatives (parents, siblings, and children) should be screened. It is suggested that second-degree relatives (aunts, uncles, cousins, and grandchildren above the age of puberty)

should also be screened if they have symptoms. If other family members are found to be affected, more individuals will need to be screened. Generally, we do not recommend screening children under age 12. It can be difficult to obtain youngsters' cooperation in order to perform the tests, and there is a low likelihood of finding abnormalities in children below this age.



SAECG Normal Values (Adult)
(Noise level should be $<0.3\mu\text{V}$)

	Normal	Patient With ARVD
Filtered QRS duration (msec)	<114 msec	139 msec
RMS voltage of terminal 40 msec	>20 μV	13 msec
LAS or duration of terminal QRS <40 μV	<38 msec	46 μV

This signal-averaged ECG, recorded with a 40–250 Hz filter, shows a prolonged QRS duration and late potentials.

Management of ARVD

Management is individualized, based on the patient's cardiac test results and symptoms, and directed at treating their ventricular arrhythmias.

Treatment Options. Management may involve (1) anti-arrhythmic drug therapy, (2) catheter ablation, and/or (3) placement of an implantable cardiac defibrillator (ICD). To date, there have been no prospective trials to determine either the relative safety and efficacy of these approaches or the optimal anti-arrhythmic agent for treating ARVD-related arrhythmias.



The most commonly used anti-arrhythmic medications in patients with ARVD are beta blockers, sotalol, and amiodarone. Several studies have reported that class 1C anti-arrhythmic drugs, such as flecainide, also can be useful.

Catheter ablation is not relied upon as primary therapy because of the high incidence of recurrence, often from other sites, which reflects the diffuse and progressive nature of the disease. However, catheter ablation can be useful when there is one clinically predominant VT

morphology, particularly if it cannot be controlled with anti-arrhythmic drug therapy.

Placement of an implantable cardiac defibrillator is generally recommended for patients who are considered to be at increased risk for sudden cardiac death. These risk factors include (1) a prior cardiac arrest; (2) syncope due to VT; (3) evidence of moderate to severe right ventricular enlargement; (4) left ventricular involvement; (5) presentation with polymorphic VT; and (6) a family history of sudden death attributed to ARVD, particularly if more than one family member has died from this disease.

Currently, there is no consensus as to whether patients should receive a single- versus a dual-chamber ICD for treatment of ARVD. However, we generally reserve dual-chamber ICDs for ARVD patients who have experienced one or more episodes of sustained monomorphic VT, particularly if the VT rate is slow. The presence of an atrial lead can be very useful to prevent inappropriate ICD discharges for sinus tachycardia. In contrast, we prefer single-chamber devices for patients undergoing prophylactic ICD implantation.



Exercise and Stimulants. Patients with ARVD are generally advised to avoid strenuous exercise since a disproportionate number have a history of competitive athletics. High-level athletic training may put excessive strain on the right ventricle, damaging the heart muscle in patients with a genetic predisposition to ARVD. We generally encourage moderate exercise, such as walking, jogging, playing golf, or bowling. Patients also are advised to limit their exposure to stimulants and other substances known to exacerbate arrhythmias. These include alcohol, nicotine, caffeine, and certain over-the-counter and prescription medications.

Follow-Up Treatment. ARVD is a progressive condition, yet the rate of progression is unknown. We generally recommend that patients have non-invasive imaging studies at least every 2 years. Patients without ICDs should repeat all of the non-invasive testing at this interval to check that their risk factors for a life-threatening arrhythmia have not increased. Other imaging modalities include radionuclide gated blood pool scans, which can also provide quantitative information useful for long-term follow-up of right ventricular function.

For patients with ICDs, echocardiography is the preferred imaging method. These patients also should have their device checked every 3 to 4 months and should see their cardiologist or electrophysiologist at least once a year.

Long-Term Outlook. The long-term outlook is good for most people who have been diagnosed with ARVD. A majority of patients have stable heart function over several decades. Some patients have periods of increased arrhythmias, sometimes referred to as “electrical storms,” that may require changes in medications or repeated ablations. It is uncommon for patients with ARVD to develop such severe dysfunction that a heart transplant would be necessary. Studies performed before the use of defibrillators and newer medications found a 95% survival rate 5 years post-diagnosis. Today, we believe that most people who die from ARVD were not diagnosed prior to their death.

Further Research

A number of aspects of ARVD remain poorly understood. For instance, the natural history of the disease is not clearly defined, and except for Naxos disease, the identification of the genes is incomplete. Because the disease is difficult to diagnose, there is concern that patients are both underdiagnosed and overdiagnosed. The optimum therapy for symptomatic patients is not known.

Multidisciplinary Study of Right Ventricular Dysplasia.

The National Institutes of Health awarded funding for a 5-year study led by Dr. Frank Marcus from University of Arizona (clinical), Dr. Wojciech Zareba from University of Rochester (data management), and Dr. Jeffrey Towbin from Baylor College of Medicine (genetics). The primary goal is to identify 100 patients with definite ARVD (probands). Each of these patients will be evaluated with standardized non-invasive and invasive tests to confirm the diagnosis. In addition, all of their first-degree relatives will be enrolled for standardized cardiac testing. Genetic studies will be carried out in an effort to find the causative genes. Clinical and genetic characterizations of these individuals and their family members should improve diagnostic techniques, leading to more accurate risk

stratification and, ultimately, therapies to treat the disease rather than its symptoms.

This grant utilizes expert core labs to centrally analyze diagnostic tests, including echocardiograms (Dr. Michael Picard, Harvard Medical School, Boston, Massachusetts), angiograms (Dr. Thomas Wichter, University of Muenster, Germany), biopsies (Dr. Gaetano Thiene, University of Padua, Italy), magnetic resonance images (Dr. David Bluemke, John Hopkins Hospital, Baltimore, Maryland), and ECGs (Dr. Wojciech Zareba, University of Rochester, Rochester, New York). The study aims to develop better quantitative methods to assess right ventricular function in order to enhance the specificity and sensitivity of the cardiac testing for ARVD. The testing for patients and family members is clinically indicated and is not experimental. While patients' medical insurance should cover the costs of these evaluations, the grant provides limited funds for patients without adequate insurance.

Eleven clinical centers in the United States and one in Canada will evaluate and enroll patients and family members in the study. If you have a patient who has one

or more features of ARVD (see the Appendix), please contact one of the clinical centers listed in this brochure. Once accepted into the study, subjects will need to go to an enrolling center for imaging and invasive studies. The patient and referring physician will benefit from this enrollment by having expert evaluation of diagnostic tests provided by specialized core labs. The clinical information gained from the cardiac testing will be supplied to the referring physicians, and the referring cardiologist can perform the follow-up care and forward data, such as ECGs and ICD interrogations, to the study.

ARVD Patient Registry. The Johns Hopkins ARVD Program is managing a patient registry that is available to all patients with ARVD who choose not to participate in the Multidisciplinary Study of Right Ventricular Dysplasia. In addition, patients with known ARVD who have ICDs and those who cannot be enrolled in the Multidisciplinary Study also can join this registry. The goal is to study the clinical characteristics and outcomes of patients with ARVD. This registry also should provide pilot data for future studies of ARVD. To refer patients for this registry, please contact the Johns Hopkins ARVD Clinic Office at 410-502-7161.

European ARVD Registry. The European Union is funding an ARVD patient registry whose goals are to (1) validate the diagnostic criteria, (2) assess the natural history, (3) determine the risk stratification for sudden death and poor prognosis, and (4) evaluate the efficacy of anti-arrhythmic drug therapies. If you have patients from Europe, you may want to contact:

Andrea Nava, MD (Italy) Tel: 0039 039 8762176

Thomas Wichter, MD (Germany) Tel: 0049 251 8347585

Guy Hugues Fontaine, MD (France) Tel: 01 45 21 25 94

William J. McKenna, MD (United Kingdom) Tel: 0044 208 7255012

Nikos Protonotarios, MD (Greece) Tel: 0030 28523234

Information Resources. Additional research studies are being conducted at Johns Hopkins Hospital and elsewhere. A number of Web sites, including WWW.ARVD.COM and WWW.ARVD.ORG, provide information about ARVD for patients and physicians. An educational brochure about ARVD written for patients and their families also is available. For more information please contact us.

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The information in this brochure is accurate as of September 2002.

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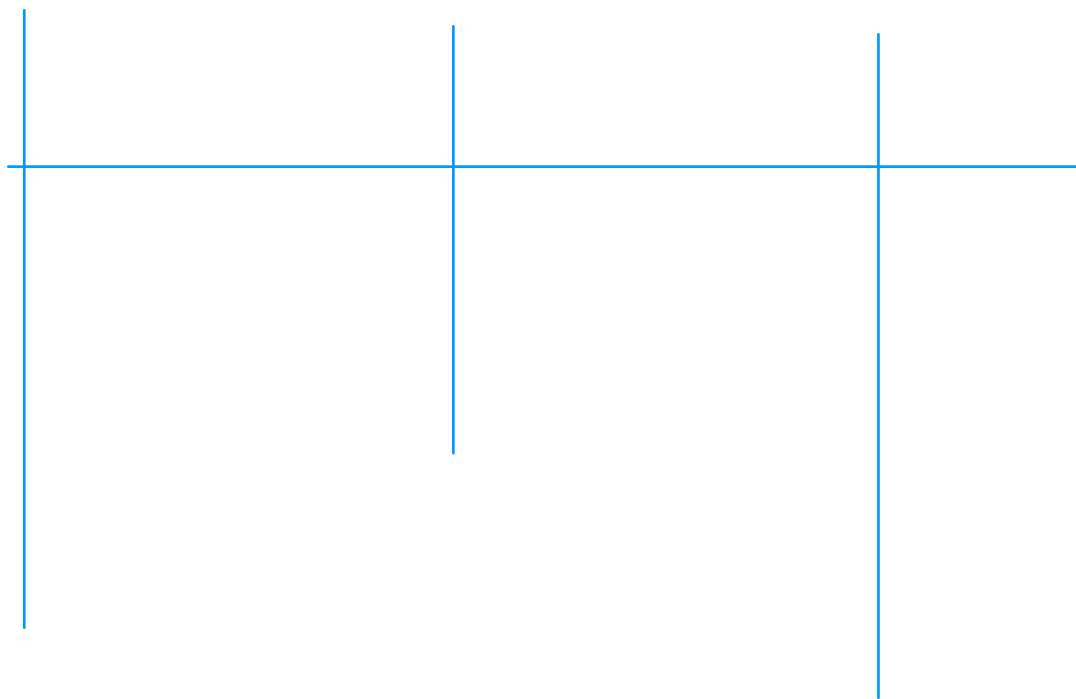
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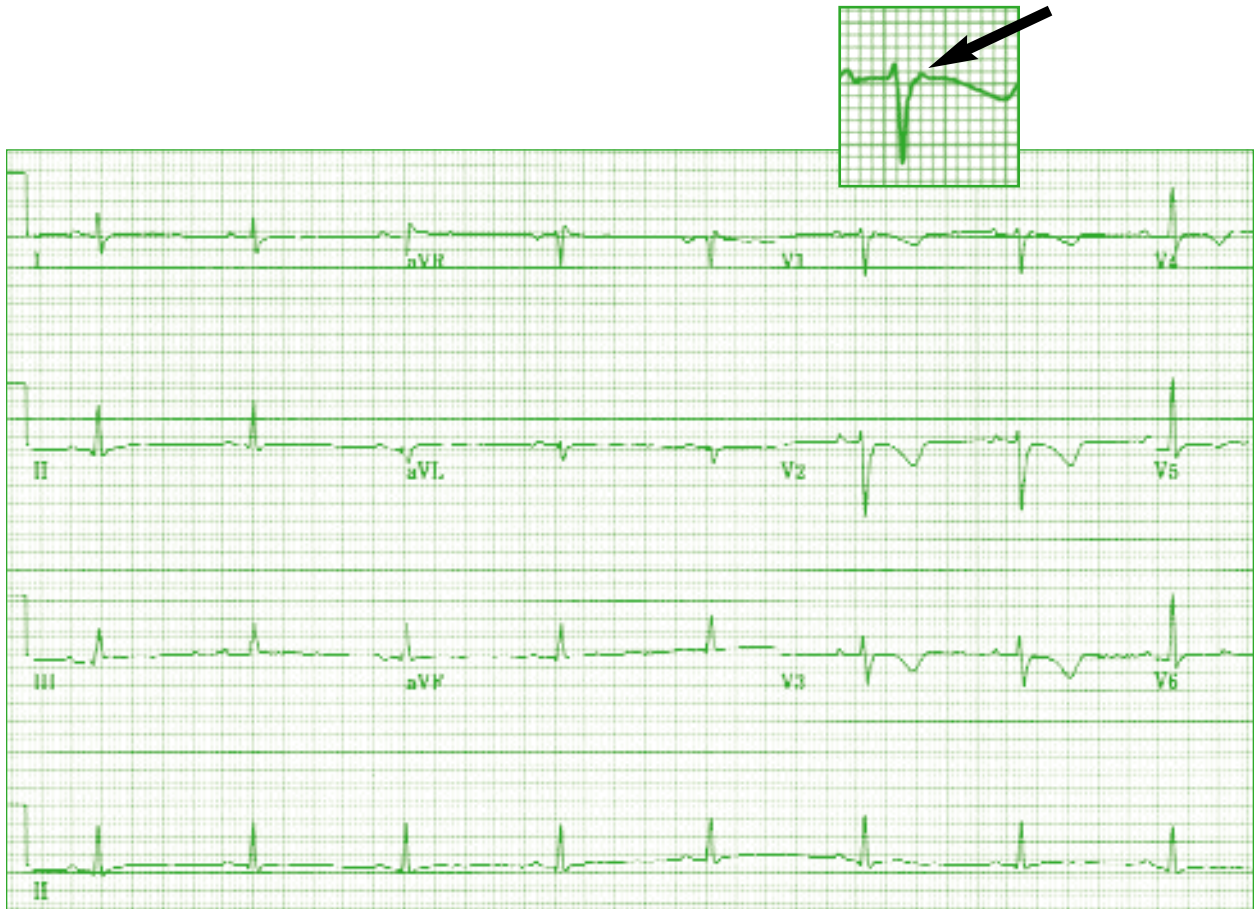
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12-lead ECG showing inverted T-waves V1–V5, QRS duration >110 msec in V1–V3, and epsilon wave in V1.

Diagnostic Criteria for ARVD

The diagnosis of ARVD is established by the presence of 2 major or 1 major and 2 minor or 4 minor criteria from these categories

	Major Criteria	Minor Criteria
Structural or Functional Abnormalities	<ol style="list-style-type: none"> 1. Severe dilation and reduction of RVEF with mild or no LV involvement 2. Localized RV aneurysm (akinetic or dyskinetic areas with diastolic bulging) 3. Severe segmental dilation of the RV 	<ol style="list-style-type: none"> 1. Mild global RV dilation and/or EF reduction with normal LV 2. Mild segmental dilation of the RV 3. Regional RV hypokinesis
Tissue Characterization	Infiltration of RV by fat with presence of surviving strands of cardiomyocytes	
ECG Depolarization/Conduction Abnormalities	<ol style="list-style-type: none"> 1. Localized QRS complex duration >110 msec in V₁, V₂, or V₃ 2. Epsilon wave in V₁, V₂, or V₃ 	Late potentials on signal-averaged ECG
ECG Repolarization Abnormalities		Inverted T-waves in right precordial leads (in V ₁ through V ₃ above age 12, in the absence of RBBB)
Arrhythmias		<ol style="list-style-type: none"> 1. LBBB VT (sustained or non-sustained) on ECG, Holter, or ETT 2. Frequent PVCs (>1,000/24 hours on Holter)
Family History	Family history of ARVD confirmed by biopsy or autopsy	<ol style="list-style-type: none"> 1. Family history of premature sudden death (< age 35) due to suspected ARVD 2. Family history of clinical diagnosis based on present criteria

Appendix

Note: ETT = exercise stress test; PVCs = premature ventricular contractions; RVEF = right ventricular ejection fraction.

Source: Adapted from W.J. McKenna et al., 1994, "Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy," *British Heart Journal*, 71:215–218.

The Multidisciplinary Study offers a prime opportunity to collect and analyze data that could improve diagnostic techniques and lead to therapies for treating ARVD instead of its symptoms.

