Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

A Multidisciplinary Study: Design and Protocol

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Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C) is a relatively newly recognized disease. A clinical profile of patients with this condition was first published in 1982.1 In that report, it was observed that the majority of patients were male. Patients presented with ventricular tachycardia of left bundle-branch block morphology. An enlarged right ventricle due to fibrofatty infiltration of the right ventricular free wall and a familial association were noted. It was considered to be a rare disease of unknown cause. Since then, it has been diagnosed with increasing frequency and has been reported to account for 3% to 5% of unexplained sudden cardiac death under the age of 65 years.2,3 Evidence of the disease is found in 30% to 50% of family members who are studied by noninvasive tests, including ECG, echocardiography, and signal-averaged ECG.4,5 It has been suggested that MRI may also be used for diagnostic purposes, but this remains controversial.6,7 Six genetic loci have been identified: ryanodine receptor (RyR2),8 plakoglobin (JUP),9 and desmoplakin (DSM).10 There is autosomal dominant transmission with all the genetic forms except Naxos disease8 and Carvahal syndrome,11 both of which have autosomal recessive transmission. These 2 autosomal recessive disorders are variants of ARVD/C that are associated with skin and hair abnormalities. The cardiac presentation in Carvahal syndrome is that of a left ventricular cardiomyopathy and arrhythmias.

With the recognition that ARVD/C is frequently familial and can cause arrhythmic death, the clinical challenge is how to definitively identify individuals with ARVD/C who have mild or minimal structural abnormalities of the right ventricle. Definite identification of minimal structural abnormalities of the right ventricle can be difficult because of the irregular shape and asymmetrical contractile pattern of the highly trabeculated right ventricle.12 Some of these individuals may be family members who may or may not have premature ventricular beats. The ventricular ectopy can be asymptomatic. Others may present with nonsustained ventricular tachycardia. A young individual resuscitated from sudden cardiac death who has no overt evidence of structural heart disease must also be suspected of having ARVD/C. The most frequent ventricular arrhythmias in young people arise from the right ventricular outflow tract. Evaluation for ARVD/C, usually by a series of diagnostic tests, should be considered in individuals with ventricular arrhythmias from the right ventricular outflow tract. Treatment for patients diagnosed with ARVD/C is empirical. There is incomplete knowledge of factors that might permit accurate risk stratification to determine which patient should be treated with an implantable cardioverter defibrillator.13

Because of the relative rarity of this disease and the difficulty and importance of establishing the diagnosis, and to obtain further information regarding risk stratification and treatment of this disease, a multidisciplinary study of ARVD/C was initiated under the leadership of Dr Frank Marcus (University of Arizona, Tucson, Ariz) and has been funded by the National Heart, Lung, and Blood Institutes.

Objectives

The specific aims of the Multidisciplinary Study of RVD/C are as follows: (1) to establish a North American ARVD/C Registry enrolling ARVD/C patients and their family members, based on standardized diagnostic test criteria, in a prospective longitudinal follow-up study; (2) to determine the genetic background of ARVD/C by identifying chromosomal loci and specific gene mutations associated with this disorder; (3) to determine the influence of the genotype on the clinical course of patients with ARVD/C and explore phenotype-genotype associations that will contribute to improve diagnosis, risk stratification, and therapy; and (4) to develop quantitative methods to assess right ventricular function to enhance the specificity and sensitivity of the diagnosis of ARVD/C.

Design

The Multidisciplinary Study of ARVD/C represents a collaborative effort of research groups from the University of Arizona, Baylor College of Medicine, and the University of
Rochester, in cooperation with enrolling centers and several expert groups serving as core laboratories. Figure 1 shows the organizational structure of the study. The study uses a World Wide Web-based operation that was developed at the University of Rochester under the leadership of Wojciech Zareba, MD, and Mary Brown, MS. This system facilitates management of all aspects of the study, including patient screening, enrollment, data collection and encryption, phenotypic classification, quality control, and coordination of this complex multicenter study. Figure 2 shows the design of the study.

Patients suspected of having ARVD/C will be screened in enrolling medical centers, geographically distributed in the United States and Canada. They will undergo a series of noninvasive tests according to specifically developed standardized protocols that include an ECG, ambulatory ECG monitoring, signal-averaged ECG, and MRI. If the data are consistent with the diagnosis of ARVD/C using the task force criteria,14 the patient will be qualified for enrollment and will be required to have invasive testing, including right ventricular angiography, right ventricular biopsy, and electrophysiology testing (if not done before enrollment). Blood will be sent to the Genetic Center Laboratory under the direction of Dr Jeffrey Towbin (Houston, Tex), who will be collaborating closely with Dr Gian Antonio Danieli (Padua, Italy) to identify causative genes. Myocardial tissue samples from endomyocardial biopsy will be screened for viral RNA. Experts in the respective core laboratories will analyze and interpret the tests. On the basis of the results of these tests, the patient will be classified as being phenotypically affected, borderline, or unaffected. Patients will be treated by their own physicians and followed up by yearly contact.

If enrolled probands are diagnosed as having ARVD/C on the basis of core laboratory evaluation, then first-degree relatives will be asked to undergo noninvasive screening and submit blood for genetic study. If cardiac abnormalities suggestive of ARVD/C are found in first-degree relatives by noninvasive testing, it will be recommended that the family members undergo complete diagnostic evaluation, including invasive testing.

**Flow Design of Screening, Enrollment, Data collection and Analysis**

ARVD/C subject is identified in one of the North American Enrolling Centers and the clinical information is sent via web system to the Tucson ARVD/C Center (Web-based registry log of all referred subjects)

Based on review of the clinical information, Dr. Frank Marcus and the associates at the Tucson ARVD/C Center categorizes the ARVD/C subject as:

Eligible for enrollment based on presence of the Task Force Criteria.

Not eligible: Task Force Criteria not present (subject kept in the registry log)

**Clinical and Diagnostic Test Data Collection in Enrolling Centers**

![Diagram](image-url)
Task Force Criteria for Diagnosis of Right Ventricular Dysplasia/Cardiomyopathy

I. Global and/or regional dysfunction and structural alterations*
   Major
   Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) LV impairment.
   Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging).
   Severe segmental dilatation of the right ventricle.
   Minor
   Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle.
   Mild segmental dilatation of the right ventricle.
   Regional right ventricular hypokinesia.

II. Tissue characterization of wall
   Major
   Fibrofatty replacement of myocardium on endomyocardial biopsy.
   Minor
   Inverted T waves in right precordial leads (V2 and V3) in people aged >12 years, in absence of right bundle-branch block.

III. Repolarization abnormalities
   Major
   Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1-V3).
   Minor
   Late potentials (signal-averaged ECG).

IV. Depolarization/conduction abnormalities
   Major
   Left bundle-branch block type ventricular tachycardia (sustained and nonsustained) by ECG, Holter, or exercise testing.
   Frequent ventricular extrasystoles (>1000/24 hours) (Holter).

VI. Family history
   Major
   Familial disease confirmed at necropsy or surgery.
   Minor
   Familial history of premature sudden death (<35 years) due to suspected right ventricular dysplasia.
   Familial history (clinical diagnosis based on present criteria).

The diagnosis of ARVD/C would be fulfilled by the presence of 2 major, 1 major plus 2 minor, or 4 minor criteria from different groups. LV indicates left ventricular.

An important part of this study is the evaluation of the diagnostic task force criteria that were proposed in 1994 (Table). These guidelines represent an important landmark in establishing minimal criteria for this diagnosis. The Task Force recognized that there is no single test that is diagnostic of ARVD/C. A combination of major and minor criteria were proposed but have not been evaluated prospectively. There were no protocols prepared for imaging the right ventricle by echocardiography, angiography, or MRI. Interpretation of contraction abnormalities observed by these imaging modalities is largely subjective and requires considerable technical and interpretive expertise. In the present study, imaging of the right ventricle by the above modalities will be performed according to protocol and interpreted in core laboratories. As part of this study, techniques are being developed to quantify right ventricular structure and function. Although the percentage of abnormal test findings can be compared with another, the diagnostic accuracy of these imaging tests will require gene identification of the proband and family members.

Identification of genes for the typical clinical form of the disease is challenging. First, phenotypic identification is difficult. Second, a significant percentage of patients have sudden death, which limits the size of the pedigrees for study. Incomplete penetrance and variable expressivity are pronounced in this condition, which makes gene identification a challenge. Two of the genes that have been identified are associated with atypical variants of the disease. Recently, a third gene has been identified in a dominant form of ARVD that causes a mutation in desmoplakin, a cellular adhesion protein. This recent finding should facilitate further gene localization. The identification of the gene(s) will have tremendous diagnostic impact and hopefully will provide an explanation as to why ARVD/C is primarily seen in the right ventricle. With the completion of the Human Genome Project and a potential understanding of the “final common pathway,” we anticipate improvement in the ability to identify these disease-causing genes.

This integrative research project offers a substantial prospect of expanding the clinical knowledge regarding ARVD/C and of localizing the genetic mutations responsible for this disorder. Physicians are urged to refer patients suspected of ARVD/C to one of the principal investigators of this study (Figure 1). For further details, please refer to the following World Wide Web sites: www.arvd.org or www.arvd.com. An ARVD/C study is now under way in Europe under the direction of Gaetano Thiene (Padua, Italy) using the same data forms and a parallel computerized database to facilitate collaboration between the North American and European operations. Physicians in Europe with patients who are suspected of having ARVD/C are encouraged to contact the following enrolling physicians: Dr Guy Fontaine (Paris, France), Dr William J. McKenna (London, UK), Dr Andrea Nava (Padua, Italy), and Dr Thomas Wichter (Muenster, Germany).

References


**KEY WORDS:** arrhythmia ■ electrophysiology ■ cardiomyopathy ■ genetics ■ imaging
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