Prospective Evaluation of Relatives for Familial Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Reveals a Need to Broaden Diagnostic Criteria

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OBJECTIVES	We sought to ascertain the prevalence and mode of expression of familial disease in a consecutive series of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).
BACKGROUND	Autosomal-dominant inheritance is recognized in ARVC. The prevalence and mode of expression of familial disease in consecutive, unselected families is uncertain.
METHODS	First- and second-degree relatives of 67 ARVC index patients underwent cardiac evaluation with history and examination, 12-lead and signal-averaged electrocardiogram (ECG), two-dimensional and Doppler echocardiography, metabolic exercise testing and Holter monitoring. Diagnoses were made in accordance with published criteria.
RESULTS	Of 298 relatives, 29 (10%; mean age 37.4 ± 16.4 years) had ARVC. These were from 19 of the 67 families, representing familial involvement in 28%. Of these affected relatives, 72% were asymptomatic, 17% had ventricular tachycardia (sustained VT 10%, nonsustained VT 7%) and 21% had left ventricular involvement. A further 32 relatives (11%; 37.7 ± 12.4 years) exhibited nondiagnostic ECG, echocardiographic or Holter abnormalities. Fifteen of these relatives were from families with only the proband affected, and inclusion of this subset of relatives would have resulted in familial ARVC in 48% of index cases. Four additional relatives (1% to 3%) fulfilled diagnostic criteria for dilated cardiomyopathy without any features of right ventricular disease.
CONCLUSION	By using current diagnostic criteria, familial disease was present in 28% of index patients. A further 11% of their relatives had minor cardiac abnormalities, which, in the context of a disease whose mode of inheritance is autosomal dominant, are likely to represent early or mild disease expression. We advocate that the current ARVC diagnostic criteria are modified to reflect the broader spectrum of disease that is observed in family members. (J Am Coll Cardiol 2002;40:1445–50) © 2002 by the American College of Cardiology Foundation

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a disease of the right ventricle characterized by fibrofatty replacement of the myocardium (1). Although clinical genetic studies have indicated that the disease may be autosomal-dominantly inherited with age-related and variable penetrance (2), only a small number of disease-causing mutations have as yet been identified (3,4).

To facilitate the clinical diagnosis of ARVC, an international task force has proposed a series of diagnostic criteria based on electrocardiographic and morphologic features (5). Theoretically, the same criteria might be used to identify relatives who also have ARVC; however, the experience of similar criteria in diagnosing hypertrophic (6) and dilated cardiomyopathies (7) has shown that many relatives have phenotypic abnormalities that, although "nondiagnostic," are nevertheless indicative of disease. The aim of this study

was to determine the prevalence of cardiac abnormalities in the relatives of a large population of consecutively referred patients with ARVC to estimate the prevalence of familial disease and to evaluate the utility of the published diagnostic criteria in family screening.

METHODS

Diagnostic criteria. Index ARVC cases and their relatives were evaluated in accordance with criteria defined by a task force of the European Society of Cardiology and International Society and Federation of Cardiology (5). The task force criteria rely on the demonstration of right ventricular structural and functional features, depolarization/repolarization electrocardiographic abnormalities, demonstration of arrhythmias originating from the right ventricle, fibrofatty infiltration of the right ventricular myocardium and evidence of familial disease. The criteria are subdivided into major and minor features, major criteria being abnormalities deemed more specific for ARVC. A combination of: 1) two major, 2) one major plus two minor, or 3) four minor features are consistent with a positive diagnosis of ARVC. Relatives were categorized into three groups after

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Abbreviations and Acronyms

ARVC/D	=	arrhythmogenic right ventricular cardiomyopathy/dysplasia
FS	=	fractional shortening
LBBB	=	left bundle branch block
LV	=	left ventricle
LVEDD	=	left ventricular end-diastolic diameter
NSVT	=	nonsustained ventricular tachycardia
RV	=	right ventricle
SAECG	=	signal-averaged electrocardiography
SCD	=	sudden cardiac death

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cardiac evaluation. Those fulfilling the task force diagnostic criteria for ARVC were labeled as affected relatives. Relatives with an isolated, minor ARVC criterion were labeled as having *probable* ARVC. Relatives without any features of disease were considered *unaffected*. Dilated cardiomyopathy was diagnosed according to World Health Organization criteria (1). Left ventricular (LV) enlargement was defined as a left ventricular end-diastolic dimension (LVEDD) of >112% predicted value corrected for age and body surface area (8). Functional impairment of the LV was diagnosed when a depressed fractional shortening of <25% was present but with cavity dimensions within the predicted range.

Probands. At St. George's Hospital Medical School there has been an ongoing program of evaluating families of patients diagnosed with primary cardiomyopathies. Since 1990, 75 index patients that have fulfilled the task force criteria for ARVC have been evaluated. These patients were referred from the Department of Clinical Cardiology and secondary care centers. Postmortem cases (with fibrofatty replacement of the right ventricular myocardium) were also included.

Relatives. A detailed pedigree of the family of each index patient was assembled, and permission was sought to invite first-degree relatives (parents, siblings and children) and, where appropriate, second-degree relatives for cardiovascular evaluation. Probands and family members were counseled by specialist nurses before the cardiac evaluation. Ethical approval for the study was obtained from the Local Research Ethics Committee.

Cardiac evaluation. After obtaining informed consent, relatives underwent history and clinical examination, 12-lead electrocardiogram (ECG), signal-averaged electrocardiography (SAECG), two-dimensional trans-thoracic and Doppler echocardiography, 24-h Holter monitoring and maximal upright cardiopulmonary exercise testing. Blood was taken and stored for future genetic studies after informed consent.

Historical evaluation. This evaluation involved the subjective assessment of cardiac symptoms. Palpitations were defined as an awareness of the heart beating faster or harder. Syncope was defined as an episode of sudden onset loss of consciousness with spontaneous recovery. Presyncope was defined as the sensation of impending loss of consciousness associated with the feeling of dizziness or lightheadedness.

Echocardiography. Two-dimensional and Doppler echocardiography was performed using an Acuson 128 XP/10 (Mountain View, California), GE Vingmed system V (GE Ultrasound Europe, Horten, Norway) or a Hewlett-Packard Sonos 1000 (Hewlett-Packard, Andover, Massachusetts) by experienced hospital technicians in an outpatient setting. Standard views for M-mode and two-dimensional studies were obtained, and conventional techniques were used for assessing the left atrium and ventricle (9). Evaluation of structural and functional abnormalities of the right atrium and right ventricle (RV) was undertaken using an established protocol (10). This involved assessment of the RV for local or global dilation and reduced function as well as wall motion abnormalities (hypokinesia, akinesia and dyskinesia) and aneurysms.

SAECG. The SAECG was performed using a MAC VU (Marquette Electronics Inc., Diagnostic Division, Milwaukee, Wisconsin). Time domain analysis was obtained in the bandpass filter 40 to 250 Hz with the following parameters evaluated: filtered QRS interval duration, low-amplitude signal duration and root mean square (RMS) of the voltage in the last 40 ms of the filtered QRS (RMS40). The signal averaged ECG was considered positive for late potentials when at least two of the following parameters were abnormal: filtered QRS duration >114 ms, low-amplitude signal duration >38 ms and RMS40 <20 μV (11). Patients with bundle branch block were excluded from time-domain analysis.

Ambulatory ECG monitoring. Twenty-four hour ambulatory monitoring was performed during unrestricted daily activities using the Marquette Holter recording system on two channels (Marquette Electronics Inc., Diagnostic Division). Computer-assisted analysis was performed using the Marquette series 8000 laser Holter and laser Holter XP system. The frequency of ventricular ectopy and its morphology was noted. Nonsustained ventricular tachycardia (NSVT) was defined as a run of three or more consecutive beats at a rate of ≥120 beats/min, lasting <30 s and sustained VT defined as a consecutive run of beats ≥30 s.

Exercise testing. Exercise testing was performed in the upright position on a Sensormedics ergometrics 800 S cycle ergometer (Ergoline, Bitz, Germany), using a ramp protocol ranging from 10 to 15 W/min (selected to ensure adequate stress and avoid premature fatigue) in a quiet air-conditioned room with an average temperature of 21°C and full resuscitation facilities. An experienced cardiologist, nurse and senior technician supervised each test. Before the test all relatives underwent a 3-min practice run at zero work rate.

Endomyocardial biopsies. Biopsies were initially performed as part of the assessment of eight index patients and three relatives. They were discontinued as a routine part of evaluation because sampling error has been shown to occur as a result of the segmental nature of the disease, and the

Table 1. Clinical Characteristics of Index Patients, Affected Relatives and Relatives With Probable ARVC

	Deceased Index Patients	Live Index Patients	Affected Relatives	Probable ARVC
Number in category	44	31	29	32
Age (yrs)	27.9 ± 9.2	35.3 ± 13.1	37.4 ± 16.4	37.7 ± 12.4
Male:female (%)	66:34	68:32	72:28	28:72
Cardiac symptoms	–	31 (100%)	8 (28%)	5 (16%)
Palpitations	–	25 (81%)	6 (21%)	5 (16%)
Presyncope	–	15 (48%)	1 (3%)	0
Syncope	6 (14%)*	12 (39%)	3 (10%)	0
NSVT	–	9 (29%)†	2 (7%)	1 (3%)
Sustained VT	–	20 (64%)	3 (10%)	0
Evidence of LV involvement	–	6 (19%)	6 (21%)	0

*Episode of syncope within 1 month of death. †Index cases demonstrating only NSVT. (%) Represents percentage value within each subgroup.

ARVC = arrhythmogenic right ventricular cardiomyopathy; LV = left ventricle; NSVT = nonsustained ventricular tachycardia; VT = ventricular tachycardia.

septum, which is sampled in preference to the right ventricular free wall for safety reasons, is relatively spared in ARVC (12,13).

Statistical analysis. Continuous variables are expressed as mean value ± 1 SD. Discrete variables are shown as percentages. Chi-squared analysis was used to test for associations between dichotomous variables. With continuous variables, group means were compared with the unpaired Student *t* or Mann-Whitney *U* test if the variable did not fulfill the normality assumption. A value of p < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences (SPSS, version 9.0).

RESULTS

Index patients. Of 75 consecutive index patients (age 31 ± 11.4 years, range 11 to 60 years), presentation with sudden cardiac death (SCD) occurred in 44 (59%), with a diagnosis established at autopsy. The majority of live and SCD index patients were male (21/31, or 68% and 29/44, or 66%, respectively; Table 1) . The SCD individuals presented at a younger age than the live patients (age 27.9 ± 9.2 vs. 35.3 ± 13.1 years; p < 0.05). Six (14%) of the deceased patients had experienced syncope during the month before their death. All 31 of the live patients presented with cardiac symptoms: 10 (32%; 46 ± 12 years) presented with syncope, 2 (6.5%; 26 and 38 years) with aborted SCD secondary to ventricular fibrillation, 17 (55%; 37.6 ± 11.2 years) with palpitation/presyncope (8 with palpitations only and none with presyncope) and 2 (6.5%; 18 and 60 years) with heart failure. Ventricular tachycardia (VT) of left bundle block (LBBB) morphology had been documented in 29 (94%) of the 31 live patients (monomorphic sustained VT in 20, or 65%, and, NSVT in 9, or 29%). One index patient from the live group died during the study period at age 21, 3 years after diagnosis. This patient had declined an automatic internal cardioverter defibrillator after syncopal episodes and

sustained ventricular tachycardia were documented. LV involvement was detected in six (19%; 33 ± 16.4 years) live cases (LVEDD 58.5 ± 9.1 mm, fractional shortening [FS] 20.6 ± 8.1%). One of the patients presenting with heart failure underwent cardiac transplantation at age 28, 10 years after the initial diagnosis.

Relatives. The families of 67 of the 75 index cases with ARVC consented to cardiac evaluation. Of the remaining eight, four families were not residing in the United Kingdom and so were unavailable for cardiac evaluation, and four families did not wish to undergo assessment. The total number of relatives who underwent cardiac evaluation was 298 (4.4 ± 4 per family). Their mean age was 35.5 ± 17.9 years, 45% were males and 194 (65%) were first-degree relatives.

Affected relatives. Twenty-nine relatives (10%; 37.4 ± 16.4 years) fulfilled the task force criteria for ARVC (Table 1). These affected relatives were from 19 of the 67 families evaluated; thus, familial involvement was present in 28% of index cases. No single family demonstrated a significantly increased number of affected relatives, the largest number being three in two families. Two of the affected relatives had already been diagnosed with ARVC before attending our institution, after presentation to their local hospitals with sustained monomorphic VT. Twenty-one (72%) of these were male. The prevalence of individual task force criteria are shown in Table 2. Ventricular arrhythmias were observed in 15 (52%). VT of LBBB morphology was documented in five (17%) and were all males aged 34.8 ± 2.9 years. There was no association between age or a positive SAECG and the occurrence of VT. Analysis of the diagnostic criteria among index patients and affected relatives did not demonstrate a specific intrafamilial phenotype (i.e., the presence of a particular electrocardiographic or echocardiographic abnormality did not run through a family).

Relatives with probable ARVC. Thirty-two (11%, 37.7 ± 12.4 years) relatives (Table 1) had isolated, minor criteria detectable on cardiac evaluation, of which 23 (72%) were female. There was no segregation of cases within any one family. There was no significant difference in age between this subgroup of relatives and the live index patients or affected relatives. Fifteen of these probable ARVC patients were from 13 families in whom only the index patient was affected. Inclusion of these probable ARVC relatives resulted in a familial prevalence of ARVC in 48% of index cases. The most frequent criteria in this group were electrocardiographic with T-wave inversion in 13 (41%) and a positive SAECG in 10 (31%). One female relative (3%), aged 36, had documented NSVT on Holter monitoring (Table 1). A further 10 (3%) of the total relatives had >100 ectopics of LBBB morphology recorded on Holter monitoring over 24 h, with seven (2%) of these having >200 ectopics over that period.

LV abnormalities. LV involvement in the absence of any other cardiac disease was present in 6 (21%) affected relatives (39.2 ± 14.2 years; five males) with LV dilation in

Table 2. Task Force Criteria Present in Live Index Patients, Affected and Probable Affected Relatives

Diagnostic Criteria	Live Index Patients (n = 31)	Affected Relatives (n = 29)	Relatives with Probable ARVC (n = 32)
Family history			
Confirmed at necropsy or surgery	–	27 (93)	26 (81)
Premature sudden death (<35 years) caused by suspected ARVC	9 (29)	7 (24)	5 (16)
Clinical diagnosis based on present criteria	–	–	–
ECG depolarization/conduction abnormalities			
Epsilon waves	1 (3)	0 (0)	0 (0)
Localized prolongation (>110 ms) of the QRS complex (V_1–V_3)	6 (19)	7 (24)	0 (0)
Late potentials seen on signal averaged ECG	18 (58)	23 (79)	10 (31)
Repolarization abnormalities			
Inverted T waves in right precordial leads (V_2 and V_3)	20 (64)	13 (45)	13 (41)
Tissue characterization of walls			
Fibrofatty replacement of myocardium on endomyocardial biopsy	2/8	0/2	0/1
Global and/or regional dysfunction and structural alterations			
Severe dilatation and reduction of RVEF with no (or only mild) LV impairment	14 (45)	1 (3)	0 (0)
Localized RV aneurysms	3 (10)	0 (0)	0 (0)
Severe segmental dilatation of the RV	1 (3)	0 (0)	0 (0)
Mild global RV dilatation and/or EF reduction with normal LV	8 (26)	11 (38)	1 (3)
Mild segmental dilation of the RV	0 (0)	3 (10)	0 (0)
Regional RV hypokinesia	1 (3)	3 (10)	3 (9)
Arrhythmias			
LBBB type VT (sustained or non-sustained) on: ECG	18 (58)	1 (3)	0 (0)
Holter monitoring	6 (19)	2 (7)	1 (3)
During exercise testing	6 (19)	2 (7)	0 (0)
Frequent ventricular extrasystoles (more than 1,000/24 h) on Holter monitoring	13 (42)	11 (38)	2 (6)

Numbers in parentheses indicate the percentage within each group. Major ARVC Task Force diagnostic criteria are shown in bold.

ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricle; RV = right ventricle; RVEF = right ventricular ejection fraction.

three and depressed fractional shortening in three (mean LVEDD 56.2 ± 3.4 mm, FS 24.1 ± 7.6%). There was no significant difference in age between those affected relatives with LV involvement and those with normal LV function. An additional four (1% to 3%) relatives (three males, one female, 46 ± 12 years) from three families had dilated cardiomyopathy (mean LVEDD 64 ± 2 mm, mean FS 17.6 ± 5.5%). Two had previously presented to hospital with symptoms of heart failure. RV structural or functional abnormalities were absent, and no ventricular tachycardias were documented in this group.

In summary, 61 (21%) of 298 relatives demonstrated at least one minor criterion from the task force criteria after cardiac evaluation, and a further four (1% to 3%) had dilated cardiomyopathy (Table 3).

DISCUSSION

Prevalence of familial ARVC and mode of disease expression. This is the first study to prospectively determine the prevalence of cardiovascular abnormalities in the relatives of consecutive, index ARVC patients. The application of published task force diagnostic criteria demonstrated evidence of ARVC in 28% of families. When all cardiovascular abnormalities, including LV involvement were considered, 48% had evidence for familial disease. This suggests that familial disease is common and that the spectrum of disease is wider than previously thought. Several studies

have evaluated cardiovascular abnormalities in relatives, but these have been performed in selected families (14) or in small numbers of probands (15). As a result, the prevalence of familial ARVC has until now only been an estimate (2,5,16).

As in previous studies, the phenotypic features of ARVC in this study were more common in males, with females representing less than one-third of the affected relatives (17,18). The average age at diagnosis was 37.4 (±16.4) years, but because the majority were asymptomatic, the time of phenotypic disease expression cannot be accurately defined. The male predominance in this disease remains

Table 3. Cardiovascular Abnormalities Detected on Evaluation of Relatives

ARVC Criteria	Number of Relatives (%)
Abnormal ECG	31 (10.4)
Abnormal signal-averaged ECG	33 (11.1)
RV abnormalities on echocardiogram	22 (7.4)
Ectopy >1,000/24 h	13 (4.4)
Ventricular tachycardia	6 (2)
Dilated cardiomyopathy	4 (1.3)
Total number of relatives with abnormalities on investigation	65 (22)

Total number relatives = 298.

ARVC = arrythmogenic right ventricular cardiomyopathy; ECG = epsilon waves, localized prolongation of the QRS complex (V_1–V_3) and T-wave inversion in the right precordial leads; VT = sustained or non-sustained ventricular tachycardia; RV = right ventricle.

unexplained, particularly as ARVC is autosomally inherited, although interestingly, the probable ARVC group consisted predominantly of females (72%). This may represent gender-related incomplete penetrance or indicate that additional environmental/genetic factors maybe necessary for complete disease expression. X-linked disease has not been reported, and examination of our pedigrees did not support this mode of inheritance.

Task force diagnostic criteria in the context of familial ARVC. During the evaluation of families, a significant proportion of relatives (11%) were found to have isolated, minor cardiac abnormalities that did not fulfill the task force criteria for a diagnosis of ARVC. This group was labeled as having probable ARVC. The most common findings were electrocardiographic with T-wave inversion in the right precordial leads in 41%, positive SAECGs in 31% and NSVT documented in 3%. Structural or functional RV abnormalities were uncommon and observed only in 12% of these relatives. Given that the mode of disease inheritance is autosomal dominant, ECG abnormalities in first-degree relatives are likely to represent early disease or mild cardiomyopathy. If this were the case, it would suggest a much higher prevalence of familial ARVC than previously thought. This would be analogous to the findings of isolated LV enlargement or reduced fractional shortening observed in relatives of patients with familial dilated cardiomyopathy (7) and the presence of electrocardiographic and mild echocardiographic abnormalities observed in first-degree relatives in hypertrophic cardiomyopathy (6). An important implication of this study is that there is a subset of relatives who are not recognized by the present diagnostic criteria. The task force criteria were designed to help standardize the diagnosis of ARVC. The criteria were reached by expert consensus opinion, based primarily on tertiary center experience with symptomatic index cases with sustained arrhythmias and information derived from patients presenting with SCD. As a consequence, the criteria are highly specific but presently lack sensitivity when evaluating asymptomatic patients and relatives with incomplete expression. Their application in the evaluation of familial disease may therefore lead to the underestimation of true disease prevalence. For example, the presence of >1,000 extrasystoles/24 h is designated as a minor criterion, but this figure is arbitrary and based on a more severely affected index group. It is probable that ventricular ectopy of 200 or more extrasystoles observed in a proportion of our relatives represents a manifestation of underlying disease. We therefore advocate that the present diagnostic criteria should be modified in recognition of a broader spectrum of familial disease expression. We propose that in the context of proven ARVC, a first-degree relative with a positive SAECG, or a minor ECG, Holter or echocardiographic abnormality from the present diagnostic criteria should indicate familial involvement (Table 4). In addition, we advocate that the frequency of ectopic activity accepted as a marker of disease expression should be reduced from 1,000 to 200 extrasystoles over a

Table 4. Proposed Modification of Task Force Criteria for the Diagnosis of Familial ARVC

ARVC in First-Degree Relative Plus One of the Following:	
1. ECG	T-wave inversion in right precordial leads (V$_2$ and V$_3$)
2. SAECG	Late potentials seen on signal-averaged ECG
3. Arrhythmia	LBBB type VT on ECG, Holter monitoring or during exercise testing
	Extrasystoles >200 over a 24-h period*
4. Structural or functional abnormality of the RV	Mild global RV dilatation and/or EF reduction with normal LV
	Mild segmental dilatation of the RV
	Regional RV hypokinesia

*Previously >1,000/24-h period in task force criteria.
ARVC = arrythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; EF = ejection fraction; LBBB = left bundle branch block; RV = right ventricle; SAECG = signal-averaged electrocardiography; VT = ventricular tachycardia.

24-h period. The modification of the diagnostic criteria will hopefully assist in the correct classification of affected family members, which is of vital importance for genetic analyses aimed at identifying linkage to a particular locus as well as help to identify those who are potentially at risk from serious arrhythmic events. Ultimately, only the advent of genetic testing for familial ARVC will allow the true interpretation of these abnormalities and provide the gold standard for diagnosis.

Study limitations. Cardiac evaluation of all first-degree family members was not performed in all families either because of family members being unavailable or unwilling to undergo testing; thus, complete ascertainment was not obtained, which predisposes toward the underreporting of familial disease. With regards to the investigative tests, the assessment for structural and functional abnormalities of the RV highlights the weakest aspect of the present diagnostic tests. Despite the well-recognized difficulties in imaging the RV, transthoracic echocardiography remains the first-line imaging modality because it is noninvasive and can be used for serial assessments. However, it is unable to characterize tissue, and subtle wall motion abnormalities may not be detected. Cardiac magnetic resonance offers the potential for improved imaging of the RV but at the present time is not routinely used because of cost and specificity concerns (19,20).

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