Clinical Profile and Long-term Follow-up of 37 Families With Arrhythmogenic Right Ventricular Cardiomyopathy

Andrea Nava, MD,* Barbara Bauce, MD,* Cristina Basso, MD, PhD,† Michela Muriago, MD,* Alessandra Rampazzo, BSc, PhD,‡ Carla Villanova, MD, PhD,* Luciano Daliento, MD, FACC,* Gianfranco Buja, MD,* Domenico Corrado, MD,* Gian Antonio Danieli, BSc,‡ Gaetano Thiene, MD†
Padua, Italy

OBJECTIVES
We sought to define the clinical picture and natural history of familial arrhythmogenic right ventricular cardiomyopathy (ARVC).

BACKGROUND
Arrhythmogenic right ventricular cardiomyopathy is a myocardial disease, often familial, clinically characterized by the impending risk of ventricular arrhythmias and sudden death.

METHODS
Thirty-seven ARVC families of northeast Italy were studied. Probands had a histologic diagnosis of ARVC, either at autopsy (19 families) or endomyocardial biopsy (18 families). Protocol of the investigation included basal electrocardiogram (ECG), 24-hour ECG, signal-averaged ECG, stress test and two-dimensional Doppler echocardiography. Invasive evaluation was performed when deemed necessary.

RESULTS
Of the 365 subjects, 151 (41%) were affected, 157 (43%) were unaffected, 17 (5%) were healthy carriers, and 40 (11%) were uncertain. Mean age at diagnosis was 31 ± 13 years. By echocardiography, 64% had mild, 30% had moderate, and 6% had severe form. Forty percent had ventricular arrhythmias, 49 were treated with antiarrhythmic drugs, and two were treated with implantable cardioverter defibrillators. Sport activity was restricted in all. Of the 28 families who underwent linkage analysis, 6 mapped to chromosome 14q23-q24, 4 to 1q42-q43, and 4 to 2q32.1-q32.3. No linkage with known loci was found in four families and 10 had uninformative results. During a follow-up of 8.5 ± 4.6 years, one patient died (0.08 patient/year mortality), and 15 developed an overt form of ARVC.

CONCLUSIONS
Arrhythmogenic right ventricular cardiomyopathy is a progressive disease appearing during adolescence and early adulthood. Systematic evaluation of family members leads to early identification of ARVC, characterized by a broad clinical spectrum with a favorable outcome. In the setting of positive family history, even minor ECG and echocardiographic abnormalities are diagnostic. (J Am Coll Cardiol 2000;36:2226–33) © 2000 by the American College of Cardiology

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary myocardial disease frequently associated with left bundle branch block (LBBB) ventricular arrhythmias and sudden death in young people (1–5). Familial forms have been reported since 1982 (1,6–8), and in 1988 we published a study of nine families with ARVC, suggesting a pattern of autosomal dominance and variable penetrance with a polymorphic phenotype (7). Several loci have been found so far, suggesting a genetic heterogeneity (9–14). None of the involved gene defects has yet been identified, and a role for apoptosis in provoking the progressive death of myocytes has been postulated (15). More recently, a defect of the gene for plakoglobin has been found in the recessive form associated with palmoplantar keratoderma (16).

Many questions remain unanswered, including the true incidence, the age at onset and the rate of progression of the disease. Moreover, clinical diagnosis, natural history and risk stratification remain challenging. Some subjects are asymptomatic all their life, while others present with arrhythmic sudden death as the first manifestation of the disease. Congestive heart failure (CHF), which may mimic dilated cardiomyopathy and require heart transplantation, is an unusual manifestation (17).

Thirty-seven families affected by ARVC from northeast Italy were systematically studied and followed up over a long period in order to clarify these issues.

METHODS
Definition. According to World Health Organization classification (18), ARVC is “characterized by progressive fibrofatty replacement of right ventricular (RV) myocardium, initially with typical regional and later global RV and some left ventricular (LV) involvement, with relative sparing of the septum. Familial disease is common, with
autosomal dominant inheritance and incomplete penetrance; a recessive form has been described. Presentation with arrhythmias and sudden death is common, particularly in the young.

**Criteria for diagnosis.** Published criteria for ARVC (19) are subdivided into major and minor criteria and are classified into six categories based on the identification of the following: 1) global and/or regional dysfunction and structural alterations, 2) fatty or fibrofatty replacement of the RV free wall, 3) repolarization abnormalities, 4) depolarization/conduction abnormalities, 5) arrhythmias, and 6) family history. The diagnosis of ARVC is based on the presence of two major criteria; one major, plus two minor criteria; or four minor criteria. Subjects examined before publication of these criteria were retrospectively reviewed.

Family history is a major criterion when there is autopsy evidence of ARVC in a family member, and a minor criterion when there is a history of sudden death in a family member ≤35 years with suspected or clinically diagnosed ARVC.

**Study population.** The study began in 1980 and enrolled 37 families affected by ARVC. Eleven of these families have been the object of clinical and genetic studies previously reported (5,7–10,12). There were 365 members (201 male, 164 female), mean age 28.6 ± 12.7 years. Mean follow-up duration was 8.5 ± 4.6 years (range, 2 to 18 years).

All the probands had a histologic diagnosis of ARVC, either at autopsy or at RV endomyocardial biopsy (four to five samples from the free wall).

In 19 families, the proband (13 male and 6 female, mean age 27 ± 10.5 years) died at a young age, and the diagnosis was made at autopsy. Eight of the 19 probands who died suddenly have been reported in previous pathologic publications (2,4). In the remaining 18 families, the proband (14 male and 4 female, mean age 25 ± 10 years) is still alive and presented with ventricular arrhythmias: nonsustained ventricular tachycardia (VT) in 8, sustained VT in 9 and ventricular fibrillation (VF) in one case. These 18 patients underwent RV and LV angiography, as well as RV endomyocardial biopsy, which were all diagnostic for ARVC.

**Study protocol.** The following noninvasive investigations were routinely performed: clinical examination, chest X-ray, 12-lead electrocardiogram (ECG), 24-h ambulatory ECG, signal-averaged ECG (SAECG), stress test and two-dimensional and Doppler echocardiography. The use of SAECG and two-dimensional echocardiogram was started in 1985; thus, subjects not previously evaluated with these tests had these investigations thereafter.

Forty-seven affected family members with either sustained or nonsustained VT had catheterization and contrast angiography with endomyocardial biopsy and electrophysiologic studies. Results of these investigations have been reported previously (20–25).

Patients were classified as affected or unaffected. Subjects with minor clinical findings, insufficient for diagnosis using the Task Force criteria (21), were classified as uncertain. Based on pedigree analysis, patients without clinical evidence of the disease but able to transmit it to their progeny were classified as healthy carriers.

During follow-up, patients who had a history of sustained VT, nonsustained VT or frequent premature ventricular beats (PVBs) were assessed every six months by clinical examination, ECG, 24-h ambulatory ECG, SAECG and echocardiography; the remaining patients were evaluated every 12 months. Subjects classified as uncertain were assessed every 12 months, and unaffected subjects were assessed every 12 months if age ≤25 years and every 24 months if age 25 to 35 years, to eventually leave the follow-up after the age of 35 years. The echocardiogram was done with a phased-array ultrasound system (Hewlett-Packard model 1500) with duplex 2.0 to 2.5-M/Hz transducer for imaging, spectral Doppler and color flow mapping, including M Mode, two-dimensional and Doppler echocardiography as previously described in detail (26–29). Examinations were evaluated independently by two observers for the presence of abnormal wall motion and regional structural abnormalities in the RV and LV, including size and ejection fraction. Agreement of interobserver analysis for segmental wall motion was found in 98% of the visualized segments; discrepancies were resolved by consensus.

Patients affected were subdivided by echocardiography investigation into three groups according to RV end-diastolic volume (RVEDV): 1) mild form—a normal or slightly increased RVEDV (<75 ml/m²) with localized hypokinetic or akinetic areas, in the presence or absence of trabecular disarrangements and thickened, hyperechogenic or dense moderator band; 2) moderate form—a 75 to 120 ml/m² RVEDV with localized hypokinetic or akinetic and/or dyskinetic areas and/or trabecular disarrangement and thickened, hyperechogenic or dense moderator band; 3)
severe form—an RVEDV $\geq 120 \text{ ml/m}^2$ with widespread akinetic and/or dyskinetic areas of the RV and diastolic bulging.

A SAECG was performed using a MAC 15 system (Marquette Inc.; Milwaukee, Wisconsin). Time-domain analysis was obtained in each patient using three different filters at 25, 40, and 80 Hz. Methods have been previously reported in detail (20,25). A SAECG was not obtained in patients with bundle branch block (QRS duration $\geq 110 \text{ ms}$). The normal values were (95% confidence interval) for the 25-Hz filtered QRSD, $120 \text{ ms}$, HFLA, $40 \text{ ms}$, RMS, $25 \mu V$; for the 40-Hz filtered QRSD, $118 \text{ ms}$, HFLA, $40 \text{ ms}$, RMS, $20 \mu V$; for the 80-Hz filtered QRSD, $106 \text{ ms}$, HFLA, $34 \mu V$, RMS, $12 \mu V$.

The SAECG was considered positive when at least two parameters were abnormal at one filter setting.

Other clinical testing (24-h ambulatory ECG, hemodynamic study with endomyocardial biopsy, exercise stress test, electrophysiologic study) has been described previously (22–24). The exercise stress test was performed as a provocative test of arrhythmias. Ventricular arrhythmias recorded at standard ECG, during 24-h Holter monitoring or during stress test examination, were subdivided into the following: 1) VF; 2) sustained VT; 3) nonsustained VT; 4) repetitive PVB couplets and triplets; and 5) frequent PVBs (>30/h) (25).

DNA studies and linkage analysis. In 28 families, a molecular genetic study was performed by linkage analysis. Genomic DNA from available family members was extracted from blood samples according to the salting-out procedure. A set of polymorphic markers closely linked to ARVD1 (arrhythmogenic right ventricular dysplasia) locus, to ARVD2, to ARVD3, to ARVD4 and to ARVD5 was analyzed by polymerase chain reaction amplification according to previously reported methods (9–14). Products were mixed with an equal amount of formamide buffer, separated on denaturing polyacrylamide gels, and the gels were silver stained. Alleles were scored and haplotypes were generated. Two-point lod scores between ARVD and these marker loci were calculated with the MLINK program of the LINKAGE package (vs. 5.2). Lod scores were calculated for two different values of penetrance: 70% and 95%.

Results. The chi-square or Fisher exact test was used to assess the significance of differences between subgroups. Two-tailed p values < 0.05 were regarded as statistically significant.

RESULTS
Among the 365 subjects, 151 (41.3%) were found to be affected. Ninety-four were male (62%), and 57 were female (38%) ($p = 0.02$), with a gender ratio of 1.6:1 (vs. 1:1 of the remaining family members). One hundred fifty-seven (43%) individuals were unaffected. Seventeen patients (5%) had no clinical evidence of the disease but could transmit it, so they were considered healthy carriers. In the remaining 40

![Figure 1. Number of affected patients among clinically evaluated subjects for each family in 37 affected families (black bar = affected patients).](image)
subjects (11%), the diagnosis was uncertain. The percentage of affected patients among clinically evaluated subjects for each family ranged from 33% to 75% (Fig. 1).

The age distribution of 19 probands who died suddenly is shown in Figure 2 (mean, 27 ± 10.5 years). Nine subjects had a previous history of syncope (47%); 13 died during effort (68%), 6 of whom had a previous syncopal episode. A 12-lead ECG tracing was available in 12 and showed negative T waves in the precordial leads at least in V1–V3 in 42%: V1–V3 in 2 cases, V1–V5 in 1 and V1–V6 in 2. Four subjects (33%) had negative T waves in the precordial leads associated with ST segment elevation >2 mm; a complete right bundle branch block (RBBB) was present in one, and an incomplete RV delay with ST segment elevation >3 mm in another case. The ECG was within normal limits in only one patient. Analysis of pedigrees of the 37 affected families showed that 20 additional subjects (14 male, 6 female) had died suddenly at a young age (mean age, 27 ± 10 years), and 2 had died from congestive heart failure (CHF), but without postmortem investigation.

Clinical picture. Among the 132 living affected patients, the disease has never been diagnosed in infancy, and only twice under the age of 10 years (4 and 6 years old, respectively). According to published criteria (19), affected patients fulfilled at least the lowest score for the diagnosis of ARVC, with the following distribution: four minor criteria in 42 patients (32%); five minor criteria in 19 (14.5%); six minor criteria in three (2%); one major, plus at least two minor, criteria in 51 (38.5%); two major, plus at least two minor, criteria in 11 (8.5%); and three major, plus at least two minor, criteria in 6 (4.5%).

The mean age at diagnosis was 31 ± 13 years (range, 4 to 64 years) (Fig. 3). The surface ECG was abnormal in 62 patients (47%): RBBB in 55 patients (complete in 5 and incomplete in 50), inverted T waves in right precordial leads (V1–V3 or more) in 24, and ST segment elevation >2 mm in the right precordial leads in 18.

By comparing clinical data of the 19 probands who died suddenly and the 132 living affected patients, we found that there was a statistically significant difference only in terms of previous history of syncope (42% vs. 18%; p < 0.001).

Sixty (45%) had ventricular arrhythmias: VF in 1, sustained VT in 14; nonsustained VT in 8; PVB couplets and triplets in 16 and frequent PVBs in 8 (>30/h), all with LBBB morphology; exercise-induced polymorphic ventricular arrhythmias were recorded in the remaining 13 patients. The age at the first recording of arrhythmias (mean, 28.5 ± 12) is shown in Figure 3.

All affected patients had echocardiographic abnormalities: 64% had a mild (85 cases, age 30.3 ± 13.5 years), 30% had a moderate form (39 cases, mean age 32.5 ± 13.8 years) and 6% had a severe form of the disease (8 cases, mean age 29.3 ± 12.6 years) (Table 1). Among the 85 patients with a mild form, 60 (70%) had evidence of RV motion abnormalities (i.e., hypokinesia or akinesia) in one or more areas: the posterior wall underneath the tricuspid valve in 45, the apex in 17 and the anterolateral free wall in 5 cases; 35 subjects (41%) had morphological changes. All 39 patients with a severe form had evidence of RV motion abnormalities in one or more areas: posterior wall underneath the tricuspid valve in 24, the apex in 15 and the anterolateral free wall in 9; 24 (61%) had evidence of morphological
changes. Each of the eight patients with a severe form had severe kinetic abnormalities of the RV posterior wall underneath the tricuspid valve, associated with apical in seven and anterolateral free wall abnormalities in seven; morphological changes were present in all. Right ventricular outflow dilatation was detected in 29% of the mild forms, 51% of the moderate forms and 100% of the severe forms. Left ventricular involvement was observed in 21 patients (16%), and it was extensive only once.

Ventricular arrhythmias were present in all patients with the severe form of the disease, in 82% with the moderate form and in 23% with the mild form (Table 2).

Ninety-eight affected patients (77%) had late potentials (LPs) at least at 80 Hz filter: in 100% of patients with the severe form, in 82% with the moderate form and in 66% with the mild form. Late potentials were also present in 10 of 157 healthy subjects. Moreover, LPs were present in 75% of the affected patients with ventricular arrhythmias and in 78% of the affected patients without arrhythmias (p = NS) (Table 3).

The maximal exercise stress test induced polymorphic ventricular arrhythmias in 13 affected patients who did not have arrhythmias at rest. In four patients with sustained VT, the test triggered the same arrhythmias. Patients with arrhythmias arising from the RV outflow tract had disappearance of the arrhythmias during the test. In the remaining patients, exercise stress test ECG did not modify the arrhythmias.

All the affected patients were advised to avoid physical exercise and sports activity. Forty-nine arrhythmic patients were treated with antiarrhythmic drugs: 17 beta-blockers, 9 propafenone, 7 amiodarone, 6 sotalol, 5 beta-blockers + amiodarone, 2 beta-blockers + disopyramide, 2 flecainide and 1 disopyramide. Patients with either VF or sustained VT were treated with beta-blockers + amiodarone (5), beta-blockers + disopyramide (2), amiodarone (2), sotalol (2), and flecainide (1); the latter patient had sustained VT originating from the RV outflow tract. Patients with effort-induced polymorphic ventricular arrhythmias were treated with beta-blockers (13). Two subjects with sustained VT who did not respond to drug therapy had implantation of an automatic cardioverter defibrillator. Nine affected patients who did not have a severe form of the disease and did not have LP or monomorphic nonsustained ventricular arrhythmias, did not receive antiarrhythmic drug therapy. Radiofrequency ablation has never been performed in this series of patients.

Follow-up. The mean duration of follow-up was 8.5 ± 4.6 years (range, 2 to 18 years). Fifteen subjects (age range, 8 to 21 years; mean age, 13 ± 3 years) who were considered unaffected at the first examination, later (mean age, 19 ± 4 years) developed structural signs of ARVC at echocardiography, and seven of them showed symptomatic ventricular arrhythmias.

Seven affected patients who did not have ventricular arrhythmias at the first examination showed frequent PVBs (>30/h) during follow-up, while two patients with frequent PVBs later developed sustained VT. Seven (5%) affected patients who initially had a normal ECG tracing showed ECG changes during the follow-up. Moreover, 10% of patients later developed LP at SAECG. Four patients with a mild form (5%) progressed to moderate disease, and three

Table 1. Echocardiographic Findings in 132 Affected Family Members

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Mild Form (85 Cases)</th>
<th>Moderate Form (39 Cases)</th>
<th>Severe Form (8 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDV (ml/m³)</td>
<td>60 ± 8</td>
<td>85 ± 10</td>
<td>123 ± 14</td>
</tr>
<tr>
<td>RVEF%</td>
<td>62 ± 5</td>
<td>58 ± 6</td>
<td>43 ± 6</td>
</tr>
<tr>
<td>RV motion abnormalities (%)</td>
<td>70</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>RV posterior wall (%)</td>
<td>52</td>
<td>61</td>
<td>100</td>
</tr>
<tr>
<td>RV apical region (%)</td>
<td>20</td>
<td>38</td>
<td>87</td>
</tr>
<tr>
<td>RV anterolateral wall (%)</td>
<td>6</td>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>Morphological changes (%)</td>
<td>41</td>
<td>61</td>
<td>100</td>
</tr>
<tr>
<td>RV outflow dilatation (%)</td>
<td>29</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>LVEDV (ml/m³)</td>
<td>59 ± 10</td>
<td>66 ± 11</td>
<td>67 ± 19</td>
</tr>
<tr>
<td>LVEF%</td>
<td>62 ± 5</td>
<td>62 ± 7</td>
<td>54 ± 9</td>
</tr>
<tr>
<td>LV involvement (%)</td>
<td>7</td>
<td>25</td>
<td>62</td>
</tr>
</tbody>
</table>

RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

Table 2. Correlation Between Arrhythmias and Extent of the Disease

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Arrhythmias (%)</th>
<th>PVBs &gt;30/h</th>
<th>Repetitive PVBs</th>
<th>Nonsustained VT</th>
<th>Sustained VT</th>
<th>Effort-induced Polymorphic VT</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild form (85 subjects)</td>
<td>23</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Moderate form (39 subjects)</td>
<td>82</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe form (8 subjects)</td>
<td>100</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Couplets and triplets.

PVBs = premature ventricular beats; VA = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia.
Table 3. Late Potentials Values Correlated With the Extent of the Disease and the Presence of Arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>LP No. (%)</th>
<th>LP at 80-Hz Filter</th>
<th>LP at 40-, 80-Hz Filters</th>
<th>LP at 25-, 40-, 80-Hz Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild form (83*)</td>
<td>55 (66)</td>
<td>9</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td>Moderate form (38*)</td>
<td>37 (97)</td>
<td>3</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Severe form (6*)</td>
<td>6 (100)</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Affected patients with arrhythmias (57*)</td>
<td>43 (75)</td>
<td>6</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Affected patients without arrhythmias (70)</td>
<td>55 (78)</td>
<td>9</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>Healthy subjects (157)</td>
<td>10 (6)</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Uncertain patients (39*)</td>
<td>8 (20)</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Carriers (17)</td>
<td>1 (6)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Patients with bundle branch block (QRS duration >100 ms) were excluded from this investigation.

LP = late potentials.

with a moderate form (8%) progressed to severe RV involvement. Two patients developed LV involvement, with diffuse abnormalities during the follow-up.

During this time interval, only one patient died suddenly. He had a severe form of the disease and had stopped therapy with amiodarone on his own 20 days before death. Thus, a mortality rate of 0.08 patient/year was calculated in affected patients.

**Genetic study.** The pedigree analysis of the 37 affected families showed an autosomal dominant mode of inheritance; both males and females can carry the disease and transmit it. Among the 37 clinically evaluated families, 28 underwent linkage analysis so far. Six of them had the disease locus mapped to chromosome 14q23-q24; in two families, significantly positive lod scores were obtained with markers closely linked to ARVD1 locus. In the other four families, due to the size of the pedigrees, a lod score value >3 was not obtained, but an at-risk haplotype defined by the markers of the ARVD1 region was shared by all the affected subjects and by none of the nonaffected subjects of the same family. Four families were linked to ARVD2 locus on chromosome 1q42-q43; a lod score of 5.3 for the marker ACTN2 was obtained in one large family, while in the remaining three families, the markers of the ARVD2 region identified an haplotype invariably shared by all the affected members and by none of the unaffected members. Four families had the disease locus mapped to chromosome 2q32.1-q32.3; a maximum lod score value of 3.75 at q = 0 for the marker D2S309 was obtained, and it was possible to reconstruct an at-risk conserved haplotype. Four large families did not show linkage with any of the ARVD known loci, providing evidence of further genetic heterogeneity. The remaining 10 families have remained uninformative due to their small size.

**DISCUSSION**

This study presents the findings of the largest systematic investigation of familial ARVC studied over a long period of time.

**Clinical presentation of familial ARVC.** The clinical onset of ARVC clearly is postponed to adolescence and young adulthood, thus supporting the concept of a disease not present at birth with late phenotypic expression (1,19). In fact, none of our familial cases was diagnosed in infancy, and clinical onset, occurrence of arrhythmias and sudden death showed a peak at the age interval of 16 to 35 years.

According to echocardiographic findings, the majority (64%) had the mild form of the disease. We found that RV abnormalities were frequently segmental, mostly in the setting of normal RV volume, thus suggesting the need for a careful echocardiographic investigation, focusing the attention to the subtricuspid and infundibular region as well as to subtle structural changes before ruling out ARVC. In this regard, echocardiography is a well accepted imaging technique employed for systematic investigation of family members because it is both noninvasive and easily reproducible, compared to angiography and isotopic methods.

It is noteworthy that in our series almost half of the cases had a normal 12-lead ECG and 55% of affected patients had no ECG-documented ventricular arrhythmias. Even though the degree of “symptomatic” penetrance might be low, the “true” penetrance of the disease was higher when systematic investigation of affected families was carried out. Thus, patients could have the concealed clinical phase of the disease, even with definite RV structural changes. These patients, in whom the arrhythmogenic substrate is present but silent, may have subtle ECG and echocardiographic signs of ARVC and LP by SAECG. In the context of a positive family history, the combination of even minor ECG and echocardiographic abnormalities is diagnostic.

The type and severity of arrhythmias were positively correlated with the extent of the disease. Arrhythmias were present in all subjects with the severe form and decreased progressively in moderate and mild forms. All but one patient with the moderate-severe form had LP on SAECG. Sudden death was a frequent clinical presentation in the family history, and most of these individuals had warning symptoms and/or signs preceding the terminal event.

**Diagnostic criteria in familial ARVC.** Although either noninvasive or invasive tests can readily confirm the presence of the overt form of the disease by revealing marked dilation and/or aneurysmal bulges of the RV, in patients with minimal anatomic changes such as mild enlargement or even normal RV volume with only localized hypokinesia, clinical recognition of ARVC is elusive. This is the major challenge when dealing with clinical investigation of family
members. Because the diagnostic criteria proposed by McKenna et al. (19) have never been rigorously tested within family members where there is by definition a much higher probability of the disease, this study gave us the opportunity to check their utility also in familial forms of ARVC. Furthermore, because ARVC has an autosomal dominant pattern of inheritance, the possibility of disease in first-degree relatives is 50%, and within an affected family the likelihood that minor ECG or echocardiographic abnormalities represent disease expression is higher than it would be outside the context of proven familial disease. It is noteworthy that although all our patients had a diagnosis of ARVC according to task force criteria (19), a major criterion was present in less than half of affected patients, and one third reached only the lowest score (i.e., four minor criteria). Moreover, because clinical expression of ARVC is postponed to adolescence and young adulthood, the proposed standard criteria for diagnosis cannot be applied until after adolescent growth is completed, as supported by the late appearance of the disease during follow-up in 15 formerly unaffected patients.

**Long-term follow-up of familial forms.** In contrast with other published series dealing with the follow-up of nonfamilial forms of ARVC (30–32), we never observed familial cases with CHF, despite the existence of severe forms at echo. This might be explained by the low mean age of study population and the relatively short-term follow-up. However, long-term progression toward CHF in some patients cannot be excluded, because the pathobiology of the disease is characterized by progressive loss of myocytes with late LV involvement (16).

Occurrence of arrhythmic sudden death during the follow-up was quite rare, with a mortality rate of 0.08 patient/year. By comparing available clinical data in probands who died suddenly and in affected living patients, only a history of syncope seemed to be predictive of sudden death. Prevalence of sudden death in patients with ARVC has been variably reported in long-term follow-up studies. Arrhythmic sudden death occurred in 2 of 15 (13%) patients reported by Blomstrom-Lundqvist et al. (33) with a mean follow-up of 8.8 years. A better outcome was observed in the series by Leclercq and Coumel (34), with only 1 case of sudden death out of 39 cases during a follow-up of 8.8 years; in the series by Marcus et al. (35) there were no fatal events in 16 patients during an 8.4-year follow-up. The apparent contrast between a malignant family history and a benign follow-up in our series may be explained by early diagnosis of ARVC, exercise restriction and prompt treatment of arrhythmic forms. Moreover, the favorable outcome may depend on the fact that in more than half of families the proband died suddenly, thus leading to survival of low risk family members.

**Management of familial forms.** Because the identification of subjects who are at high risk for sudden death has been elusive, management of asymptomatic patients is still unclear, particularly in the setting of subtle morphological abnormalities. Previous cardiac arrest, recurrent syncope, severe RV and/or LV involvement and polymorphic sustained VT seem to carry a worse long-term prognosis. However, a minority of affected patients could remain asymptomatic or suddenly develop life-threatening arrhythmias and sudden death, especially upon effort. Usually we do not treat asymptomatic patients with antiarrhythmic drugs but rather recommend avoiding strenuous physical activity. In patients with ventricular arrhythmias, antiarrhythmic drug therapy might decrease the risk of sudden death, as suggested by the very low mortality rate in our series as well as in other previously reported studies (33–37). In our series, type of drug was selected on the basis of the severity of arrhythmias, extension of the disease, presence of LP at SAECG and results of electrophysiologic study. Because clinical findings that predict the long-term outcome of ARVC patients is incompletely known, up to now there have been no precise guidelines to select those who should be treated with beta-blockers, antiarrhythmic drugs or implantable cardioverter defibrillator, except for patients with sustained VT or VF, in whom programmed ventricular stimulation with serial drug testing should be performed (38).

**Genotype-phenotype correlation.** The pedigree analysis of these 37 affected families confirmed that both males and females can carry and transmit the disease. The percentage of affected subjects is almost 50% of family members, thus supporting an autosomal dominant type of inheritance with incomplete penetrance (7,8,39). Nevertheless, the prevalence of affected patients and severe forms of the disease is higher in males than females. The same male/female ratio was observed in patients who had died. It is likely that the phenotypic expression of the disease is determined not only by the genotype but also by environmental factors, favoring a higher occurrence and expression in males.

The clinical findings may differ in the genetically distinct forms of ARVC. Affected members of families with the ARVD2 locus typically had effort-induced polymorphic ventricular arrhythmias even in the setting of the mild form of ARVC (40). As in other inherited heart diseases, an influence of the genotype on the clinical manifestations and course of ARVC is likely to occur.

**CONCLUSIONS**

Systematic study of family members and long-term follow-up are bringing to light a less severe clinical form of ARVC with a more favorable outcome than previously thought. In the context of a positive family history, even subtle ECG and echocardiographic abnormalities are diagnostic for ARVC. Clinical appearance during late adolescence and young adulthood reinforces the concept of an acquired and progressive myocardial atrophy not present at birth.
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Reprint requests and correspondence: Dr. Andrea Nava, c/o Associazione Ricerche Cardiopatie Aritmiche, Via A. Gabelli, 86 - 35121, Padua, Italy. E-mail: anava@ux1.unipd.it.

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