Arrhythmogenic Right Ventricular Dysplasia
A United States Experience
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Background—Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy characterized by right ventricular dysfunction and ventricular arrhythmias. The purpose of our study was to describe the presentation, clinical features, survival, and natural history of ARVD in a large cohort of patients from the United States.

Methods and Results—The patient population included 100 ARVD patients (51 male; median age at presentation, 26 [interquartile range {IQR}, 18 to 38; range, 2 to 70] years). A familial pattern was observed in 32 patients. The most common presenting symptoms were palpitations, syncope, and sudden cardiac death (SCD) in 27%, 26%, and 23% of patients, respectively. Among those who were diagnosed while living (n = 69), the median time between first presentation and diagnosis was 1 (range, 0 to 37) year. During a median follow-up of 6 (IQR, 2 to 13; range, 0 to 37) years, implantable cardioverter/defibrillators (ICD) were implanted in 47 patients, 29 of whom received an appropriate ICD discharge, including 3 patients who received the ICD for primary prevention. At follow-up, 66 patients were alive, of whom 44 had an ICD in place, 5 developed signs of heart failure, 2 had a heart transplant, and 18 were on drug therapy. Thirty-four patients died either at presentation (n = 23: 21 SCD, 2 noncardiac deaths) or during follow-up (n = 11: 10 SCD, 1 of biventricular heart failure), of whom only 3 were diagnosed while living and 1 had an ICD implanted. On Kaplan-Meier analysis, the median survival in the entire population was 60 years.

Conclusions—ARVD patients present between the second and fifth decades of life either with symptoms of palpitations and syncope associated with ventricular tachycardia or with SCD. Diagnosis is often delayed. Once diagnosed and treated with an ICD, mortality is low. There is a wide variation in presentation and course of ARVD patients, which can likely be explained by the genetic heterogeneity of the disease. (Circulation. 2005;112:3823-3832.)

Key Words: arrhythmia ■ cardiomyopathy ■ death, sudden ■ heart failure ■ tachycardia

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy characterized by right ventricular (RV) dysfunction and ventricular arrhythmias. On pathological examination, patients with ARVD demonstrate fibrofatty replacement of the myocardium of the RV. Studies have shown that ARVD is present in up to 20% of individuals who experience sudden cardiac death (SCD) and is even more common among athletes who die suddenly. ARVD was first described in 1977 by Fontaine et al. The clinical features of 24 French patients with this condition were first reported by Marcus et al in 1982. During the ensuing 22 years, relatively few studies have been published describing the clinical features and outcomes of patients with ARVD. The great majority of these studies have involved European populations. In fact, only 2 independent series of ARVD patients from the United States, involving 20 and 12 patients, respectively, have been reported in the literature.

The purpose of this study was to describe the clinical characteristics and outcomes of a large cohort of ARVD patients from the United States. Particular attention was focused on defining the presenting symptoms, time to diagnosis, and long-term outcomes of these patients.

Methods

Patient Recruitment
Patients were identified from the Johns Hopkins ARVD registry. This registry was initiated in 1998 and prospectively enrolls patients referred to the Johns Hopkins ARVD Program with a possible diagnosis of ARVD. The study protocol was approved by the Johns Hopkin...
TABLE 1. Demographic Characteristics, Athletic Participation, and Presenting Symptoms in the Entire Patient Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diagnosed While Alive (n=69)</th>
<th>Diagnosed on Autopsy (n=31)</th>
<th>Total (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at presentation, mean±SD, y</td>
<td>30±12</td>
<td>29±15</td>
<td>29±13</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>36 (52)</td>
<td>15 (48)</td>
<td>51 (51)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>65 (94)</td>
<td>30 (97)</td>
<td>95 (95)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (1.5)</td>
<td>1 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (3)</td>
<td>...</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>1 (1.5)</td>
<td>...</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Actively involved in athletic activity</td>
<td>37 (54)</td>
<td>12 (39)</td>
<td>49 (49)</td>
</tr>
<tr>
<td><strong>Presenting symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>25 (36)</td>
<td>2 (6)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Syncope</td>
<td>21 (30)</td>
<td>5 (16)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (13)</td>
<td>...</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Near syncope</td>
<td>8 (12)</td>
<td>1 (3)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Nausea, vomiting, and diaphoresis</td>
<td>6 (9)</td>
<td>...</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Dizziness or lightheadedness</td>
<td>14 (20)</td>
<td>...</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3 (4)</td>
<td>...</td>
<td>3 (3)</td>
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<tr>
<td>Chest pain</td>
<td>2 (3)</td>
<td>...</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>...</td>
<td>23 (74)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Resuscitated from SCD</td>
<td>1 (1.5)</td>
<td>...</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>15 (22)</td>
<td>...</td>
<td>15 (15)</td>
</tr>
</tbody>
</table>

Data are represented as frequency (%) except for age at presentation, which is expressed as mean±SD.

Patient Population

The patient population was composed of 100 patients diagnosed with ARVD. The clinical features of the patients are summarized in Tables 1 and 2 (and listed for individual patients in the online-only Data Supplement Tables I and II). Sixty-nine of the 100 patients were diagnosed with ARVD...
while living (online-only Data Supplement Table I), and 31 patients were diagnosed with ARVD on autopsy (online-only Data Supplement Table II). There were 51 men. The median age at presentation was 26 (IQR, 18 to 38; range, 2 to 70) years. Ninety-five were white, 2 were black, 2 were Hispanic, and 1 was of Middle-Eastern origin. Forty-nine were routinely involved in sports or exercise. Thirty-two patients from 19 families had evidence for the familial form of ARVD, including 19 (22%) of the 87 index cases in the study population.

Presenting Symptoms
Table 1 summarizes the presenting symptoms among the 100 patients in this series. Palpitations, syncope, and death were the most common presenting symptoms (27%, 26%, and 23%, respectively). Fifteen patients were asymptomatic at the time of first presentation. ARVD was suspected in these patients on the basis of family history suggestive of ARVD or premature SCD or an abnormal ECG pattern at a routine physical examination. Fatal ventricular arrhythmia leading to SCD was the first manifestation of ARVD in 22 patients. Of these, 1 was resuscitated and survived the presenting episode of SCD, and 21 died. Two additional patients presented with death from noncardiac causes.

Characteristics of Patients Diagnosed With ARVD While Living
Summarized in Table 2 (and listed in the online-only Data Supplement Table I) are the results of clinical testing of the 69 ARVD patients who were diagnosed with ARVD while living. The diagnosis of ARVD was established on the basis of the presence of (1) 2 major criteria (n=23); (2) 1 major plus 2 minor criteria (n=36); and (3) 4 minor criteria (n=10). It is notable that only 1 patient (patient 17) had a “structurally normal” right ventricle. All patients demonstrated 1 or more ECG abnormalities characteristic of ARVD. The most common ECG abnormalities detected were delayed S-wave upstroke and T-wave inversions in 91% and 81% of the patients, respectively.

Clinical Course of Patients Diagnosed With ARVD While Living
Shown in Figure 1A and summarized in Figure 2 is the clinical course of each of the 69 patients in this series who were diagnosed with ARVD while living. Each patient is represented as a straight line, and the major events in the course of the disease are plotted by the age at which the event took place.

The median age at presentation was 29 (IQR, 20 to 36; range, 2 to 63) years. All patients except 1 presented clinically after the onset of adolescence. This patient (patient 1) was a 2-year-old white girl who presented with a syncopal episode. Her ECG demonstrated sustained monomorphic VT, which was terminated by cardioversion. She experienced another syncopal episode at the age of 3 years. The patient underwent MRI evaluation at the age of 6 years and was eventually diagnosed with ARVD on the basis of the task force criteria. An ICD was implanted at that time. The oldest patient (patient 69) was a 63-year-old white man who presented with palpitations associated with sustained VT, which was cardioverted externally. Diagnosis was established 1 year later when he developed recurrent VT. An ICD was implanted then. Neither of these patients received any ICD discharge during follow-up.

The median age at diagnosis was 33 (IQR, 26 to 43; range, 6 to 72) years, and the median time between first presentation and diagnosis was 1 (IQR, 0 to 6; range, 0 to 34) year. Among the 69 patients who were diagnosed while living, the median follow-up was 6 (IQR, 2 to 13; range, 0 to 37) years.

As shown in Figure 2, 26 patients presented with an episode of symptomatic sustained VT. Nine patients who initially presented with symptoms in the absence of documented VT subsequently developed sustained VT. After the episode of VT, 31 of these 35 patients underwent placement of an ICD, 11 of whom also underwent 1 or more catheter ablation procedure. Four of these patients were treated with drug therapy alone, 2 (patients 5 and 49) of whom experienced SCD within 3 years of presentation. One patient (patient 39) of the 22 who presented with ventricular fibrillation, was successfully resuscitated from cardiac arrest. He
received both an ICD and catheter ablations during follow-up. In addition to these 32 patients in whom an ICD was implanted after an episode of sustained VT (n=31) or aborted SCD (n=1), an ICD was implanted on a prophylactic basis in 15 patients, including 3 asymptomatic patients. Three of these 15 patients subsequently experienced appropriate ICD therapy. Of the total 47 patients who had an ICD implanted, 29 (62%) received at least 1 appropriate ICD therapy during a median of 4 (IQR, 2 to 6; range, 0 to 20) years after the ICD implantation. Among the 69 patients, there were only 3 deaths (2 SCD [patients 5 and 49] and 1 due to heart failure [patient 6]). All 3 patients had 1 or more episodes of syncope, and only 1 (patient 6) had an ICD in place at the time of death.

Figure 1. Clinical course of each of the 69 patients in this series who were diagnosed with ARVD while living (A) and 31 patients diagnosed on autopsy (B). Each patient is represented as a straight line, and the major events in the course of the disease are plotted by the age at which the event took place. The initiation of each line represents the first clinical presentation, and the termination of the line represents either a terminal event or the censoring due to the end of follow-up. The junction of the dotted line and the solid line represents the age at which the patient was diagnosed with ARVD. The following symbols represent different events that occurred in the history of the disease: ●, syncope; ▲, first documented VT; ✗, termination of VT by external cardioversion; ◐, catheter ablation of VT; ⊙, ICD implantation; ●, appropriate ICD therapy; ◄, onset of heart failure; ◇, heart transplant; and +, death.
Clinical Characteristics of Patients Diagnosed With ARVD on Autopsy

Summarized in Figure 2 (and listed in online-only Data Supplement Table II) are the characteristics of 31 patients (15 male) who were diagnosed with ARVD for the first time at autopsy. The median age was 24 (IQR, 16 to 39; range, 13 to 70) years. Twenty-nine of these patients experienced a cardiac arrest. Eighteen patients (62%) were involved in routine activity, 9 (31%) were involved in active exercise, 1 (3.5%) was pregnant, and 1 (3.5%) was in bed at the time of death. The cardiac arrest was the first symptom of ARVD in 21 patients. Two patients died of a condition other than ARVD but were diagnosed with ARVD on autopsy.

On gross examination, the mean heart weight was 357±68 (range, 250 to 500) g in women and 417±106 (range, 240 to 650) g in men (P=0.08). RV dilatation was moderate to severe in 9 patients (29%) and mild in 20 patients (65%). The mean RV wall thickness was 2.7±2.2 mm. On microscopic examination, RV myocardial loss, either complete or with few myocardial cells, was seen in all heart specimens. Fatty infiltration of RV myocardium (except for a thin endomyocardial layer and trabeculae) alone was seen in 9 hearts (29%). Fibrofatty infiltration was seen in 22 hearts (71%). Inflammatory infiltrates were seen in 7 (23%) of the heart specimens.

Eight of these 31 patients had other symptoms before death. Importantly, 5 of these 8 patients experienced 1 or more episodes of syncope. The median time between presentation and death in these 8 patients was 1.5 (IQR 1 to 3, range 0 to 4) years. The age and the sequence of events that occurred in each of the patients diagnosed on autopsy are represented in Figure 1B.

Survival and Heart Failure in ARVD

As shown in Figure 2, 31 patients in the cohort of 100 experienced SCD. Six patients developed right-sided heart failure, one of whom (patient 6) progressed to biventricular heart failure and died at the age of 27 years while awaiting heart transplant. Two patients died of causes other than ARVD. Two patients (patients 37 and 62) underwent cardiac transplantation after developing incessant VT. One of these patients (patient 62) also had significant right-sided heart failure. Sixty-six of the ARVD patients in this series were alive at last follow-up, of whom 44 had an ICD in place, 20 were on medical therapy alone, and 2 had a transplanted heart.

Figure 3 shows the Kaplan-Meier curve for survival free from ARVD-related deaths in the 100 patients since their first clinical presentation (causes of death other than ARVD were excluded). In the entire patient population, there were 32 deaths from cardiac causes (31 SCD and 1 from biventricular heart failure). In 24 of the 31 patients diagnosed on autopsy, SCD was the first presenting symptom. The remaining 7 SCDs all occurred within 5 years of first presentation. None
of the 7 patients had an ICD implanted at the time of death. Only 3 deaths occurred among the 69 patients who were diagnosed with ARVD while living. Two of these deaths were SCDs, which occurred within 5 years of first clinical presentation in patients without an implanted ICD, and 1 death occurred as a result of biventricular heart failure and occurred 14 years after the first clinical presentation. The patient had an ICD implanted at the time of death and was awaiting a heart transplant.

Figure 4 shows the results of Kaplan-Meier survival analysis by age for the 100 patients in the study with the following outcomes: (1) any symptom, (2) ventricular arrhythmia, (3) heart failure, and (4) cardiac death. Shown in Figure 4A are the results of this analysis in the 69 patients diagnosed while living, and shown in Figure 4B are the results of the analysis in the 31 patients who were diagnosed on autopsy. The survival curves show that none of these events are common before the onset of adolescence.

Among the 69 patients diagnosed while living, half of the ARVD patients had their first clinical presentation (experienced symptoms) by the age of 32 years. The development of symptoms mirrors the development of ventricular arrhythmia, and half the individuals develop VT by the age of 41 years. Heart failure was a rare event, occurring in ~25% of patients who survive up to the age of 56 years. Death also was extremely rare among those diagnosed while living, and it is notable that only 3 patients (described above) experienced cardiac death during follow-up. The death-free survival time in 94% of this group of patients was >60 years.

The median age at first clinical presentation (24 years) among the 31 patients diagnosed on autopsy was not significantly lower than that in those diagnosed while living \((P=0.16)\). However, the median age at cardiac death (25 years) in this group was significantly lower than that in the 69 patients diagnosed while living \((P<0.001)\). The small difference between the age at presentation and the age at death reflects the fact that the majority of these patients experienced SCD as their first clinical presentation, and those who did not experience SCD as their first presenting symptom experienced it shortly after their first presentation.

When we performed Kaplan-Meier analysis after combining the entire patient population \((n=100; \text{results not shown})\), the median age at first presentation was 30 years. By the age of 60 years, nearly 50% of the patients experienced cardiac death. Heart failure was experienced by ~25% of patients who survived up to the age of 70 years.

**Discussion**

The results of this study describe in detail the presentation, clinical characteristics, and follow-up of 100 ARVD patients from the United States. This is the largest cohort of ARVD patients from the United States, and the results of this study allow us to compare the clinical features of these patients with those of the previously described European populations of ARVD patients. The results also provide important insights into the natural history and treatment of this rare but potentially life-threatening inherited cardiomyopathy.

**Prior Studies**

Since first described >20 years ago,\(^1\) ARVD has fascinated the cardiology community.\(^{20,25,26}\) The great majority of prior studies have focused on particular aspects of ARVD such as
Figure 4. Kaplan-Meier survival analysis demonstrating proportion of patients free from (1) any symptom, (2) ventricular arrhythmia, (3) cardiac death, and (4) onset of heart failure since birth among the 69 patients diagnosed while living (A) and from (1) any symptom and (2) cardiac death among the 31 patients diagnosed on autopsy (B). The numbers below the graph represent the subjects at risk of the event and those having the event in each decade of life. The numbers in parentheses represent the percentage of patients, among the total number at risk, experiencing the event.
Clinical Characteristics of ARVD Patients

Our findings are consistent with the results of prior studies that described the clinical characteristics of patients with ARVD.1,9,10 Notably, in this study, among those diagnosed with ARVD while living, >95% of patients had 1 or more ECG features of ARVD, ~70% had an abnormal SAECG, and all patients except 1 had a structurally abnormal RV. The marked similarity of clinical characteristics of ARVD between this and prior studies suggests the similarity between patients from the United States and Europe and almost certainly reflects the use of the task force criteria.

Family History

A familial pattern of inheritance of the disease was observed in 32 patients in 19 families in our series. This likely represents an underestimate of true prevalence of familial pattern because systematic screening of all family members was not performed. Furthermore, we relied on the task force criteria to establish a diagnosis of ARVD while screening family members. Hamid et al10 recently proposed that less stringent criteria be used for the diagnosis when screening family members who are likely to be evaluated at an earlier stage of the disease. The incidence of familial pattern of ARVD in our series fits within the wide range of 15% to 50% described in the literature.36,37

Clinical Course and Natural History of ARVD

The results of our study call attention to the variable clinical course experienced by patients with ARVD. First, it is notable that one half of the patients with ARVD presented with a malignant or potentially malignant ventricular arrhythmia. This fact emphasizes the importance of screening family members of patients with known ARVD. An additional 44% of the remaining patients experienced a sustained ventricular arrhythmia during the course of the disease. These findings make it clear that arrhythmic events are the most important manifestation of ARVD. This also helps explain why patients with ARVD, once treated with an ICD, have an excellent prognosis. Second, in our patient population, progression to heart failure was uncommon, occurring in <10% of patients. Only 1 patient progressed from right heart failure to a biventricular heart failure and subsequently died while awaiting a heart transplant. Prior studies have reported up to 20% incidence of heart failure among ARVD patients.13,14,32,38 The recent study published by Hulot et al32 reported a much higher incidence of death from heart failure. The difference in incidence of and mortality as a result of heart failure is probably due to the more advanced disease in the tertiary care hospitals in which the studies were conducted as opposed to the Web-based recruitment system used in our study. It is also likely that the study samples included in different studies represent different phenotypes of the disease. In fact, the study reported by Marcus et al14 which included patients from both France and the United States, showed a high incidence of heart failure among the series from France (8 of 22 patients) compared with a zero incidence among the patients from the United States. Finally, the results of our study further demonstrate that diagnosis and subsequent treatment are associated with excellent survival. Among the 69 patients diagnosed while living, only 2 experienced SCD, neither of whom had an ICD in place. Our findings differ from those reported by Hulot et al32 which indicate an overall death rate of 21 of 130 patients. This is likely explained by the lower use of ICD therapy. In fact, none of the 31 patients from our patient population who died suddenly had an ICD in place. Our data indicate that the median survival free from cardiac death in ARVD patients is ~60 years. This type of analysis has not been performed previously in ARVD patients.
Study Limitations

The patients in our study population either were referred to us because of clinical symptoms and diagnosis of ARVD or were screened because of a diagnosis of ARVD in a family member. This ascertainment bias as well as familial clustering (although the majority of the patients [87%] were unrelated probands) may have influenced the results of our study. Accordingly, the findings of our study may not be directly applicable to the entire population of ARVD patients, which may comprise a large number of patients with a milder form of the disease. The Kaplan-Meier analyses may therefore have underestimated the true event-free survival time among ARVD patients. However, because of the complexity of establishing ARVD diagnosis, lack of a single sensitive marker for the disease, and the rarity of the disease, it is virtually impossible to avoid this ascertainment bias. Another important limitation of our study lies in the fact that the study population was composed of 2 different subsets of patients: those diagnosed while living and followed prospectively (n=69) and those diagnosed on autopsy (n=31). The burden of SCD experienced by ARVD patients may have been overestimated by this selection bias. Finally, among the patients diagnosed on autopsy, although each of the histopathological specimens was evaluated by a pathologist, precise information about the extent and the distribution of the disease was not available for analysis.

Conclusion

In conclusion, the results of our study demonstrate that patients with ARVD have highly variable ages and symptoms at presentation and that most patients with ARVD experience symptomatic, potentially life-threatening arrhythmias during follow-up. Although SCD is a common presenting symptom, once diagnosed, the incidence of SCD is rare, and the overall prognosis of ARVD is excellent. This largely reflects the widespread use of ICDs in the United States. Few patients with ARVD progress to heart failure. These findings are consistent with the previously described 4 possible phases of ARVD: (1) the concealed phase; (2) an overt electric disorder; (3) RV failure; and (4) a biventricular pump failure. The onset and the duration of each of these phases vary widely among individuals. Further research is needed to identify which clinical and/or genetic factors account for the differing clinical course of ARVD patients. It is likely that the results from the North American ARVD Registry and the international ARVD registry may provide important information in the future.

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Disclosure

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References


**CLINICAL PERSPECTIVE**

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy characterized by right ventricular dysfunction and ventricular arrhythmias. The results of our study provide important insights into the presentation and clinical course of patients with ARVD. From a clinical perspective, 3 findings of this report should be highlighted. First, the results of this study demonstrate that ARVD typically presents between the second and fifth decades of life with palpitations, syncope, or sudden death. Although most patients who experience sudden death have no prior warning symptoms, an important subset of patients experience syncope before sudden death. These findings emphasize the importance of screening family members and also being alert to the potential for ARVD among patients with syncope. Second, the results of this study demonstrate that patients with ARVD, once treated with an implantable cardioverter-defibrillator (ICD), have an excellent prognosis. None of the ARVD patients who died suddenly had undergone ICD implantation. It is important to emphasize, however, that the patients in this series met the very strict task force criteria for ARVD. We do not advocate routine ICD placement in patients with only borderline or suggestive evidence of ARVD. Finally, the results of our study reveal that progression to right- or left-sided heart failure is rare, occurring in <10% of patients in this series. We are hopeful that advancements in the understanding of the genetic basis of ARVD will help to unravel many of the remaining mysteries of this disease during the next 5 years.
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