Natural History and Risk Stratification of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Background—Management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is complicated by the incomplete information on the natural history of the disease and by the lack of risk stratification for cardiovascular death. The aim of the study was the identification of risk factors related to long-term prognosis.

Methods and Results—Data were collected from 130 patients (100 men; age at onset of symptoms, 31.8 ± 14.4 years) from a tertiary center between 1977 and 2000 who fulfilled the international standardized diagnostic criteria for ARVD/C. Risk factors for cardiovascular death were determined by a logistic regression model. After a mean follow-up of 8.1 ± 7.8 years, 24 deaths were recorded, with a mean age at death of 54 ± 19 years (annual mortality rate, 2.3%). There were 21 deaths with a cardiovascular origin (progressive heart failure for 14 patients and sudden death for the remaining 7 patients). All patients who died had a history of ventricular tachycardia. Multivariate analysis showed that after adjustment for sex, history of syncope, chest pain, inaugural ventricular tachycardia, recurrence of ventricular tachycardia, and QRS dispersion, clinical signs of right ventricular failure and left ventricular dysfunction both remained independently associated with cardiovascular mortality. The combined presence of one of these risk factors and ventricular tachycardia identifies high-risk subjects for cardiovascular mortality, whereas patients without ventricular tachycardia displayed the best prognosis.

Conclusions—The information on the natural history of patients with ARVD allowed us to identify risks factors for cardiovascular mortality. An analysis of a large international registry is needed to refine these results. (Circulation. 2004;110:1879-1884.)

Key Words: cardiomyopathy ■ death, sudden ■ heart failure ■ risk factors

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited disease of the heart muscle associated with ventricular arrhythmias and sudden death. It has been reported to account for 3% to 10% of unexplained sudden cardiac death at the age of less than 65 years. Patients with ARVD are thus candidates for an active therapeutic management, including invasive electrophysiological procedures and implantation of a cardioverter-defibrillator. Since its first description more than 20 years ago, considerable progress has been made in terms of pathogenesis, genetics, and diagnosis. It is now well known that this cardiomyopathy is characterized by structural and functional abnormalities of the right ventricle caused by the replacement of the myocardium by fatty and fibrous tissue. An international registry has been initiated, and standardized diagnosis criteria have been proposed by the working group on myocardial and pericardial disease of the European Society of Cardiology and the scientific council on cardiomyopathies of the World Heart Federation.

However, ARVD manifests by means of a wide spectrum of clinical presentations, from symptomatic patients to asymptomatic relatives of patients with this cardiomyopathy. Similarly, a wide range of prognoses has been suggested, from a long-term favorable outcome to adverse events including sudden death and heart failure. Actually, incomplete knowledge on the natural history and the risk factors for cardiovascular mortality leads to empirical therapeutic strategies for ARVD patients. Therefore, we report data on the natural history and risk stratification for long-term outcome of 130 patients with this clinical entity.

Methods

Patients

Data on 163 individuals with a suspected diagnosis of ARVD were analyzed. All patients were from the cardiac arrhythmia department of Jean Rostand Hospital, Ivry sur Seine, and Pitié-Salpêtrière Hospital, Paris, France, where the diagnosis was made between 1977 and 2000. They were considered for a diagnosis of ARVD because
of a compatible history of ventricular arrhythmia, and/or compatible ECG or morphological anomalies, and/or a familial history of ARVD or sudden death.

Data were extracted from the medical record of each patient. These included demographic data (sex, race), clinical data (familial history of ARVD, initial presentation of the disease, age at onset of symptoms of ARVD, physical examination), and ECG data. The earliest 12-lead ECG and 24-hour Holter recordings (when possible before medication) were retained for analysis. For 13 patients, ECG could not be analyzed because of (1) loss of recordings (n=3), (2) immediate postventriculotomy recordings (n=9), or (3) permanent pacing (n=1). The QRS dispersion was defined as the difference between the maximum and minimum QRS values in the precordial leads.

Morphological, structural, and functional data on the right and left ventricular myocardium were assessed by noninvasive (12-lead ECG, signal-averaged ECG [25 to 250 Hz], echocardiogram, radionuclide angiography) and invasive (left and right ventriculography, coronary angiography, biopsy, and electrophysiological study) explorations. Data were analyzed by 2 investigators. The left ventricular ejection fraction was assessed by radionuclide angiography (n=63), echocardiography (n=43), or ventriculography (n=18). In 6 patients, assessment of the left ventricular ejection fraction was not available. Left ventricular dysfunction was defined as a left ventricular ejection fraction of <40%.

The diagnosis of ARVD was then established among the 163 patients according to the standardized criteria recommended by the Task Force of the European Society of Cardiology. Briefly, these criteria are subdivided into major and minor criteria and are classified into 6 categories, as follows: (1) global and/or regional dysfunction and structural alterations, (2) fibrofatty replacement of the myocardium, (3) repolarization abnormalities, (4) depolarization/conduction abnormalities, (5) arrhythmias, and (6) family history. The diagnosis of ARVD was defined according to the presence of either 2 major criteria or 1 major plus 2 minor criteria or 4 minor criteria.

Outcomes and Follow-Up
The circumstances of death were obtained from the patient’s physicians and/or patient’s family. Global mortality was then divided into cardiovascular mortality (sudden cardiac death and death as a result of heart failure) and extracardiac mortality. “Sudden cardiac death” was defined as an immediate death or a death occurring within 1 hour after the onset of symptoms without a context of heart failure.

For each patient, the follow-up period was assessed from the first visit in the cardiac arrhythmia department to May 1, 2000.

Statistical Analysis
The prevalence of demographic and cardiovascular characteristics among the patients who died of cardiovascular causes and those who remained alive or died of noncardiovascular causes was compared by use of a χ² test or Fisher’s exact test (expected count of <5) for categorical variables and a t test for continuous variables. The factors associated with cardiovascular death (P<0.10 in the univariate analysis) were retained as potential confounders. Then, a stepwise multivariate logistic regression was performed to identify those most associated with cardiovascular death using a probability value of P<0.05. Because no deaths were observed in the group of patients without ventricular tachycardia, this risk factor could not be included in the multivariate model. Survival from cardiovascular death was determined by use of the Kaplan-Meier method, and cumulative survival rates were compared by the log-rank test.

A value of P<0.05 was considered statistically significant. All statistical analyses were performed on SAS software, eighth release (SAS Institute).

Results

Patient Characteristics
Among the 163 patients with a suspected diagnosis of ARVD, 130 fulfilled the international standardized diagnostic criteria. The remaining 33 patients were excluded from the analysis.

Table 1 describes the characteristics of the overall sample. A predominance of male patients was observed (100 men versus 30 women). Palpitations were described by two thirds of the patients, a history of syncope by one third, and atypical chest pain by one quarter. There were 8 asymptomatic patients. In 4 of them, the diagnosis of ARVD was suspected in a familial context, whereas it was made in the other 4 because of frequent premature ventricular contractions of left bundle-branch block morphology discovered during a systematic examination. Mean (±SD) age at onset of symptoms was 31.8±14.4 years, and age ranged from 10 to 73 years.

There were no significant differences in age at onset of symptoms according to the symptomatology or the first manifestation of the disease (data not shown).

A history of at least 1 episode of left bundle-branch block ventricular tachycardia was the most frequent arrhythmia. It was observed in 78.5% of patients and represented the first symptom in 39% of them. An aborted cardiac death was observed in 17 patients (from ventricular fibrillation in 8 patients and from sustained hemodynamically unstable ventricular tachycardia in 9 patients). It was the first manifestation of the disease in all cases.

The ECG was spontaneously abnormal in 83.9% of the patients. T-wave inversion in the right precordial leads (V1 and V2) in the absence of right bundle-branch block was the most frequent anomaly (45.8% of the patients), whereas an epsilon wave was present in nearly one third of the patients. An abnormal signal-averaged ECG was present in two thirds of the patients. Among the 8 patients who had a right ventricular failure, 2 (25%) also had left ventricular failure. Symmetrically, among the 13 patients who had a left ventricular failure, 2 (15%) had a right ventricular failure.

Right ventricular angiography revealed signs in favor of ARVD in 89.7% of the patients. Histological examinations were performed in 22 patients using myocardial tissue from 2 autopsies, 16 ventriculotomies, and 4 septal biopsies. A fibrofatty replacement of the myocardium was observed in the samples of 20 patients. Histology was normal in the 2 remaining samples, which both correspond to biopsies from the apical and/or anterosuperior part of the septum.

Ninety-two percent of patients were treated with an antiarrhythmic therapy (including β-blockers, amiodarone, or flecainide, used alone or in combination). Ten patients received an implantable cardioverter-defibrillator. The first implantation was performed in 1994. Six of these patients had survived an aborted death related to a ventricular fibrillation or a sustained episode of ventricular tachycardia with hemodynamic compromise.

Natural History
Mean (±SD) and median duration of follow-up were 8.1±7.8 and 6.0 years, respectively. Patients with the longest follow-up period are those who were described in the first publication that contributed to the description of the disease in 1977.¹

Twenty-four patients died during follow-up, resulting in an overall mortality rate of 18.5% and an annual mortality rate of 2.3%. Mean age at death (±SD) was 54±19 years. The causes of deaths are reported in Figure 1. There were 21
cardiovascular deaths, among which 7 were sudden cardiac deaths and 14 were a result of progressive heart failure (7 ventricular tachycardia or fibrillation occurring during an acute episode of severe cardiac failure, 5 terminal heart failure, and 2 rapid deaths after a cardiac transplantation).

Two patients died of an extracardiac cause, including a car crash and a massive digestive hemorrhage. In 1 case, the cause of death remained undetermined. There were no deaths among the 10 patients who had an implantable cardioverter-defibrillator. Among these 10 patients, 6 had at least 1 appropriate shock because of recurrence of VT.

Predictors of Mortality and Risk Stratification
The characteristics of the 21 patients who died of a cardiovascular cause are compared with those of all other patients in Table 1. All patients who died of a cardiovascular cause had at least 1 episode of left bundle-branch block ventricular tachycardia. There were no deaths among the 28 patients in whom no ventricular tachycardia was documented. Both inaugural and recurrent ventricular tachycardia were associated with cardiovascular death (Tables 1 and 2).

Determinants related to cardiac failure (clinical signs of right ventricular failure and left ventricular dysfunction) were strongly associated with cardiovascular death. In univariate logistic regression (Table 2), other potential confounders of cardiovascular death were as follows: syncope, chest pain, and QRS dispersion. After adjustment for sex, history of syncope, chest pain, inaugural ventricular tachycardia, recurrence of ventricular tachycardia, and QRS dispersion, clinical signs of right ventricular failure and left ventricular dysfunction both remained independently associated with cardiovascular deaths (Table 2). No interaction was observed between these 2 factors.

To refine the risk stratification for cardiovascular death, we combined the previous risk factors and defined 3 groups of patients: group 1 included patients without ventricular tachycardia (n=28); group 2 included patients with ventricular tachycardia but no clinical signs of right ventricular

| TABLE 1. Characteristics of the Overall Sample and According to the Presence of Cardiovascular Death |
|-------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                                        | Overall Sample  | Cardiovascular Death | Survivors or Noncardiovascular Death |
|                                                        | (n=130)         | (n=21)             | (n=109)         |
| Vital characteristics                                    |                 |                  |                  |
| Male sex, %                                              | 76.9            | 76.2             | 77.1            | NS              |
| Familial history of ARVD or sudden death, %              | 28.5            | 28.6             | 28.4            | NS              |
| Age at onset of symptoms, y, mean (SD)                  | 31.8 (14.4)     | 36 (15.8)        | 30.9 (14)       | NS              |
| Clinical symptomatology                                  |                 |                  |                  |
| Asymptomatic, %                                          | 6.2             | 0                | 7.3             | NS              |
| Palpitations, %                                          | 66.9            | 61.9             | 67.9            | NS              |
| Syncope, %                                               | 32.3            | 57.1             | 27.5            | 0.008           |
| Atypical chest pain, %                                   | 26.9            | 47.6             | 22.9            | 0.02            |
| Clinical signs of right ventricular failure, %           | 6.2             | 23.8             | 2.7             | 0.003           |
| Dyspnea (NYHA >1), %                                     | 10.8            | 9.5              | 11              | NS              |
| Arrhythmia history                                       |                 |                  |                  |
| Aborted cardiac death, %                                 | 13.0            | 14.3             | 12.8            | NS              |
| Left bundle-branch block type ventricular tachycardia, % | 78.5            | 100              | 74.3            | 0.007           |
| Inaugural ventricular tachycardia, %                     | 39.2            | 61.9             | 34.9            | 0.02            |
| Recurrence of ventricular tachycardia, %                 | 41.5            | 61.9             | 37.6            | 0.04            |
| Ventricular fibrillation, %                              | 6.2             | 0                | 7.3             | NS              |
| Ventricular premature contraction >1000/24 h, %          | 30.8            | 14.3             | 33.9            | 0.04            |
| QRS dispersion >40 ms, %                                 | 40.0            | 57.1             | 36.7            | 0.08            |
| Supraventricular arrhythmia, %                           | 8.5             | 14.3             | 7.3             | NS              |
| ECG findings                                             |                 |                  |                  |
| Heart rate, bpm, mean (SD)                               | 61.0 (12.0)     | 60.0 (7.7)       | 62.0 (12.7)     | NS              |
| Epsilon-wave, %                                          | 28.0            | 35.7             | 26.9            | NS              |
| T-wave inversion in right precordial leads (V2 and V3), % | 45.8            | 42.9             | 46.1            | NS              |
| Abnormal signal-averaged ECG, %                          | 69.4            | 88.9             | 67.4            | NS              |
| Morphological findings                                   |                 |                  |                  |
| Global RV dilatation and dysfunction, %                  | 53.8            | 66.7             | 51.4            | NS              |
| Localized right ventricular aneurysms, %                 | 47.7            | 47.6             | 47.7            | NS              |
| Left ventricular dysfunction, %                          | 10.0            | 33.3             | 11.5            | 0.0001          |

*χ² test or Fisher exact test (expected counts <5) for categorical variables; t test for continuous variables.
failure or left ventricular dysfunction (n=85); and group 3 included patients with ventricular tachycardia and signs of clinical right ventricular failure and/or left ventricular dysfunction (n=17). A trend toward a gradient of risk was found from group 1 to group 3. The number of cardiovascular deaths in the 3 groups was 0 (0%) in group 1, 10 (11.8%) in group 2, and 11 (64.7%) in group 3. This corresponds to an annual mortality rate of 0% in group 1, 1.4% in group 2, and 4.7% in group 3. Figure 2 describes the cumulative survival curves for cardiovascular mortality among the 3 groups. Patients from group 1 displayed the best prognosis and differentiated early from other patients. Conversely, patients in group 3 had the worst prognosis and differentiated progressively from patients in group 2, who were at intermediate risk (P<0.05 by the log-rank test).

Discussion

In this retrospective study, we report the natural history of 130 patients suffering from ARVD. We observed that heart failure and sudden cardiac death represent the main components of overall mortality in such patients but that heart failure is twice as frequent as sudden cardiac death. A history of ventricular tachycardia, clinical signs of right ventricular failure, and left ventricular dysfunction were found to be predictors of long-term cardiovascular death. Moreover, a combination of these risk factors allowed us to identify ARVD patients at greater risk of cardiovascular death.

Natural History of ARVD

Information about the natural history of a disease is essential to define and optimize therapeutic strategies on the basis of the risk of death. However, because of the low incidence of the disease, previous studies have included small numbers of patients, resulting in a wide variation of reported death rates and causes of death.10–15 We report here the highest rate of overall and annual mortality compared with others. This may have several explanations. (1) Our cohort was based on patients addressed in a well-known cardiac arrhythmia tertiary center, and it is possible that this may have induced the inclusion of higher-risk patients. (2) This result could also be related to the wide spectrum of presentation of the disease and to a potentially high heterogeneity of prognosis among this spectrum. Accordingly, in our study, some characteristics, such as the absence of ventricular tachycardia, appear to

| Table 2: Univariate and Multivariate Analysis of Factors Predicting Cardiovascular Death |
|---------------------------------|------------------|-----------------|------------------|
| Syncope                        | 3.51             | 1.34–9.17       | 0.01             |
| Atypical chest pain            | 3.06             | 1.16–8.02       | 0.02             |
| Clinical signs of right ventricular failure | 10.99          | 2.40–50.73      | 0.0002           |
| Inaugural ventricular tachycardia | 3.04             | 1.16–7.93       | 0.02             |
| Recurrence of ventricular tachycardia | 2.69             | 1.03–7.05       | 0.04             |
| QRS dispersion >40 ms          | 2.30             | 0.89–5.95       | 0.08             |
| Left ventricular dysfunction   | 10.64            | 3.02–37.03      | 0.0002           |

*Stepwise logistic regression adjusted for syncope, chest pain, clinical signs of right ventricular failure, inaugural ventricular tachycardia, recurrence of ventricular tachycardia, QRS dispersion, and left ventricular dysfunction.
discriminate patients with better prognosis. Similarly, a favorable outcome profile (ie, mortality rate of 0.08 patient/y) was reported by Nava et al\textsuperscript{10} in a systematic study of subjects from 37 families in which 1 member was affected by ARVD.

Mortality in our patients was explained primarily by a cardiovascular origin. Sudden cardiac death accounts for one third of cardiac deaths, whereas heart failure was the cause of death for the remaining two thirds of patients. The natural history of ARVD is usually described as strongly related to the ventricular electrical instability caused by fatty replacement of myocardium. However, the progression and extension of the disease could also provoke right and/or left ventricular failure, which could lead to hemodynamic or arrhythmic death. The severity of right ventricular dysfunction, however, was not clearly related to left ventricular dysfunction. The surprising higher prevalence of deaths caused by heart failure in our study emphasizes this mechanism. Whether this finding is the natural history or reflects a shift in the cause of death because of therapeutic management of myocardium. However, the progression and extension of the disease could also provoke right and/or left ventricular failure, which could lead to hemodynamic or arrhythmic death. The severity of right ventricular dysfunction, however, was not clearly related to left ventricular dysfunction. The surprising higher prevalence of deaths caused by heart failure in our study emphasizes this mechanism.

Whether this finding is the natural history or reflects a shift in the cause of death because of therapeutic management of myocardium is an issue that requires further investigation.

**Risk Factors for Cardiovascular Death**

Our findings show that the presence of right or left ventricular dysfunction is the strongest independent predictor of cardiovascular death. Pinamonti et al\textsuperscript{14} were the first to describe a worse prognosis for patients presenting with signs of heart failure at initial examination. Le Guludec et al\textsuperscript{15} have also reported a worse prognosis in patients with right ventricular arrhythmias and left ventricular involvement. Although ARVD is an inherited disease of the heart muscle involving the right ventricle, there is now clinical and pathological evidence that the left ventricle may be progressively affected thus resulting in a biventricular failure.\textsuperscript{17} It has been reported previously that patients with a history of syncope were at higher risk of cardiovascular death. This finding is probably a marker of paroxysmal ventricular arrhythmias.\textsuperscript{11,18} However, we report here that the lack of left bundle-branch block type ventricular tachycardia identifies a small proportion of patients with ARVD who have the best prognosis. These patients were diagnosed primarily incidentally or because of a familial history of a sudden death. The extent to which they correspond to patients with an early stage of the disease was not clearly assessed.

**From Risk Stratification to Therapeutic Implications**

The main objective of management strategy is to prevent cardiovascular death, ie, arrhythmic sudden death, but also death caused by heart failure. Actually, drugs and implantable cardiac defibrillators are the 2 main therapies available for such patients. A consensus exists for the indication of an implantable defibrillator in cardiac arrest survivors. The most recent patients with such a feature were treated in this way in the present cohort, yet the treatment of the majority of patients with ARVD remains undefined. We developed a risk stratification scheme for cardiovascular death that could help physicians in choosing an optimal strategy. High-risk patients present with clinical signs of right heart failure and/or have a left ventricular dysfunction and have an history of ventricular tachycardia. These patients should be regarded as candidates for aggressive therapeutic management. Notably, in our study, we could not differentiate risk factors for arrhythmic deaths, presumably because of a lack of power.

Conversely, patients without VT are at very low risk of cardiac events. However, they should not be left unconsidered. First, the fact that most of these patients were treated by a preventive antiarrhythmic drug in the earliest stage of the disease may explain their observed good prognosis. Second, lifestyle recommendations should be still given, because these patients could remain at risk to develop further arrhythmias or heart failure in the long term, especially in effort conditions. We believe that there are 2 different mechanisms of VT. During the early phase of the disease, we observed that VT is an epiphenomenon, potentially carrying the risk of sudden death and independent of progression to chronic heart failure. However, during the late phase of the disease, severe heart failure can be responsible by itself for the occurrence of VT. In addition, some patients may develop catastrophic congestive heart failure because of a severe form of ARVD without cardiac arrhythmias.\textsuperscript{19} A surgical technique has been proposed for the treatment of patients with isolated major dilatation of the right ventricle with preserved left ventricular function.\textsuperscript{20} Finally, between these 2 extremes are patients with ventricular tachycardia but no right or left heart failure. In such patients at intermediate risk, the optimal treatment strategy remains to be defined.

**Study Limitations**

This study presents limitations that should be acknowledged. First, our cohort provides data from a monocentric tertiary center. Sudden death represents the inaugural symptom of ARVD for several subjects.\textsuperscript{3} Our results do not take this kind of patient into account. In this study, 17 of 130 patients (13%) were survivors of cardiac arrest. Therefore, our patients may not be as representative of the overall population suffering from ARVD.

Second, ARVD shared several characteristics with other cardiomyopathies, such as some form of dilated cardiomyopathy.\textsuperscript{2} In this work, we applied strict standardized diagnostic criteria of ARVD. However, histological proof was not available for all patients, and therefore, patients with other borderline arrhythmogenic cardiomyopathies may have been included.

Third, treatment was not controlled for and could have influenced the prognosis. Moreover, many changes of therapy occurred for each patient during the follow-up. In particular, 10 patients received an implantable cardiac defibrillator. This could have changed the natural history of these patients,\textsuperscript{21,22} but it is unlikely that it has substantially modified the overall results.

In conclusion, the analysis of the long-term natural history of a large cohort of patients with an ARVD allowed us, for the first time, to identify several risk factors for cardiovascular mortality. In addition to the risk of arrhythmic death, the importance of cardiac failure was outlined in the present study. This could be of some help in clinical practice and should certainly encourage further investigations for the
prevention of both arrhythmias and heart failure in ARVD patients.

Acknowledgments
This work has been supported by contract 99B0691 from the Ministere de l’Education nationale, de la recherche et de la technologie, and by the fifth framework program Research and Technology Development of the European commission “Quality of life and management of living resources” QLG1-CD-2000-01091 and INSERM AVENIR Project.

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Circulation. 2004;110:1879-1884; originally published online September 27, 2004;
doi: 10.1161/01.CIR.0000143375.93288.82
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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