Prognostic Value of Radionuclide Angiography in Patients With Right Ventricular Arrhythmias

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Background—The prognosis of patients with right ventricular (RV) arrhythmias remains uncertain. This study prospectively evaluated the prognostic value of RV and left ventricular (LV) involvement assessed by radionuclide angiography (RNA) as predictors for sudden death.

Methods and Results—Patients (n=188) with severe arrhythmias originating from the RV were followed up for a mean of 45±34 months. Data on clinical presentation, resting and stress ECG, signal-averaged ECG, 24-hour Holter monitoring, and programmed stimulation were collected along with RNA. Patients were classified as group I (n=82) with normal RNA or group II (n=106) with an abnormal RV suggestive of arrhythmogenic RV cardiomyopathy, classified as diffuse or localized disease, with or without associated LV abnormalities. During follow-up, 14 patients died suddenly, all in group II. None of the clinical and electrical data were predictive of death. An abnormal RNA study was a highly predictive factor for death (P<0.005), as well as the presence of LV abnormalities (P<0.01).

Conclusions—The present study confirms that arrhythmogenic RV cardiomyopathy is a severe disease with a high risk for cardiac death. Evidence of RV abnormalities in patients presenting with RV arrhythmias is highly predictive for sudden death, as is its association with LV involvement. (Circulation. 2001;103:1972-1976.)

Key Words: death, sudden □ arrhythmia □ radioisotopes □ cardiomyopathy

The prognosis of patients presenting with right ventricular (RV) arrhythmias such as repetitive left bundle-branch block (LBBB) ventricular tachycardia (VT) remains uncertain. Some cases are benign, without overt heart disease, symptomatic but apparently devoid of risk of sudden death (SD). In other patients, ventricular arrhythmias are associated with arrhythmogenic RV cardiomyopathy (ARVC), and SD represents a real risk, even in the concealed phase of this progressive disease.1–7 Hence, an accurate evaluation of RV functional alterations, invasive or not,8,9 may have major prognostic implications in such patients.

Our group previously reported the high diagnostic value of radionuclide angiography (RNA) with Fourier analysis in the diagnosis of ARVC compared with x-ray angiography.10–13 The crucial question is the outcome of these patients. We conducted a prospective prognostic study to determine the risk factors for sudden cardiac death in this population according to the results of their evaluation and particularly of RNA studies.

Methods

Patients

Two hundred fourteen consecutive patients investigated for severe ventricular arrhythmias in 4 cardiac arrhythmia departments entered this study, including 148 males (mean age 44±15 years, range 13 to 84 years). Criteria for inclusion were (1) symptomatic, documented, recurrent paroxysmal ventricular arrhythmias originating from the RV; (2) either sustained (SVT) or nonsustained (NSVT) VT (SVT: tachycardia >120 bpm lasting >30 seconds; NSVT: tachycardia >120 bpm lasting <30 seconds), or polymorphic or repetitive (>4 beats) RV premature contractions (VPCs) associated with syncope or faintness; and (3) absence of known or suspected left ventricular (LV) abnormalities, such as ischemic or valvular disease, idiopathic dilated cardiomyopathy, or any other origin of RV pressure or volume overload on clinical, radiological, and echocardiographic studies. Stress myocardial scintigraphy (n=13) or coronary artery angiography (n=77) ruled out coronary artery disease in cases in doubt and in patients >50 years old. Patients presenting with isolated VPCs were not included, nor were patients with toxic, metabolic, or iatrogenic ventricular arrhythmias.

The RV origin of VT was deduced from an LBBB pattern in ≥1 episode of clinical tachycardia or on the morphology of VPCs and confirmed by electrophysiological study (EPS) in 71 patients. An LBBB pattern of VT originating from the LV, such as is seen in septal myocardial infarction, was excluded because none of the patients had coronary artery disease. The following data were collected: (1) type of symptoms (palpitations, presyncope, or syncope); (2) resting ECG, classified as normal or abnormal (complete or incomplete right bundle-branch block [RBBB], negative T waves in the right chest leads, presence of epsilon waves); (3) stress test,
Radionuclide Angiography
Methodology for acquisition, processing, and interpretation of RNA studies has been published previously.14–16

Acquisition
After intravenous injection of 25 mCi of 99mTc-labeled red blood cells, acquisition was performed in 3 views: left anterior oblique 30° to 50° (best septal), right anterior oblique 20° to 0°, and left anterior oblique 70° to 90°. A 10° to 15° cranio-caudal angulation was adapted to each patient so as to optimize the separation between atria and ventricles. Sixteen ECG gated images were acquired in a 64 × 64 matrix format, with a precount of 600 000 per frame. Great care was taken to suppress premature beats during ECG synchronization, with a window threshold of 10 ms around the mean RR.

Processing
Processing was performed with a commercially available software (SMV). When undersampling of the last image had been corrected, a median 3 × 3 spatial filter was applied to the raw data. The LV diastolic and systolic regions of interest were drawn by a semiautomated detection edge algorithm, manually corrected with Fourier and Laplacian images when necessary. The RV diastolic region was manually drawn with black-and-white end-diastolic images and Fourier amplitude and phase images to avoid the atria and to include the outflow tract. The computation of the first, second, and third harmonic sine and cosine of the discrete Fourier transform of the series was performed. For the first harmonic, the usual amplitude and phase images and histogram were generated. For multiharmonic analysis, the end-systolic time image and histogram were computed by taking into account the sum of the 3 first harmonics. LV ejection fraction (LVEF) and LV segmental function were also computed.

Analysis
The first step was always a visual analysis of the cine display, taking into account end-diastolic and end-systolic deformations, qualitatively evaluating global and regional RV and LV function. Global enlargement and hypokinesia were noted as present or absent. With a segmentation in 4 segments (apex, outflow tract, inferior wall, and free wall), visual assessment of segmental wall motion noted each segment as normal, hypokinetic, akinetic, or dyskinetic. Fourier analysis was performed on amplitude images, phase images, and histograms of ventricles both together and separately, as well as on the images and histograms of end-systolic time. In each segment, a delayed contraction area was noted as present or absent.14 For quantitative analysis, the mean RV minus LV end-systolic time shift was calculated on masked regions. The mean shift was previously evaluated to be 11 ± 6 ms in normal patients and was considered abnormal if superior to 1° (mean plus 2 SDs). Two experienced observers read all the studies, and a consensus was reached in case of disagreement. Interobserver reproducibility, previously published, was 96%.14 Analysis of global and regional LV function was also performed. Normal LVEF in our department, evaluated on a previous control group, is 65 ± 10%.

Study Design
Patients were classified according to the results of the radionuclide study by both visual and Fourier analysis. Group I patients had a normal RNA: normal global and segmental function at visual cine analysis and normal visual and quantitative Fourier analysis of both ventricles. Group II patients had an abnormal RV. RV involvement was classified as diffuse in case of global RV dilation or hypokinesia, associated or not with akinetic or dyskinetic segments. It was considered localized in the presence of akinetic or dyskinetic segments separated by normal segments at visual analysis and/or a Fourier shift > 1°. The number of abnormal segments was noted, as well as the presence of an LV wall motion abnormality and the LVEF.

Statistical Analysis
Quantitative variables were expressed as mean ± SD and compared by the Wilcoxon rank sum test. Binary and categorical variables were compared by Pearson’s χ2 test or Fisher’s exact test when appropriate. All tests were 2-sided, with a 5% significance level.

Survival curves were obtained by Kaplan-Meier nonparametric estimator. Potential risks factors for SD that were tested were the presence of syncpe, abnormal resting ECG, stress ECG, Holter monitoring, SA-ECG, EPS, abnormal scintigraphy, and presence of associated LV abnormalities. Univariate analysis was performed by comparison of survival curves with Wilcoxon test. A multivariate Cox model was fitted to obtained adjusted hazard ratios.17 All prognostic variables at the 10% level in the univariate analysis were entered in the analysis. A backward stepwise model reduction procedure was performed and a likelihood ratio test used to identify the set of independent predictors. Proportional hazards hypotheses were tested graphically with the method of Grambsch and Therneau.18 All analyses were performed with SAS 6.12 (SAS Institute) and S-Plus 4.5 (MathSoft Inc) software packages.

Results

RNA in Arrhythmogenic RV Cardiomyopathy

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Study Population
All 188 patients followed up were symptomatic, presenting with palpitations (n = 92), presyncope (n = 53), or syncope (n = 43). One hundred twenty-nine patients presented with RV, 18 with NSVT, and 12 with polymorphic or repetitive VPCs associated with syncope. Resting ECG was abnormal in 42% of the patients: T-wave inversion in precordial leads occurred in 39% of patients (16.5% in group I versus 56.7% in group II, P < 0.0001), incomplete RBBB in 21% (17.7% versus 23.3%, P = NS), complete RBBB in 7.7% (6.3% versus 8.7%, P = NS), and epsilon waves in 2.7% (1.3% versus 3.9%, P = NS). SA-ECG, stress testing, 24-hour Holter monitoring, and EPS according to inclusion criteria were available in 164, 151, 161, and 179 patients, respectively.

Results of RNA Study
RNA study was normal for both RV and LV in 82 patients (group I). Mean LVEF was 64 ± 8.6%. Mean Fourier phase shift between ventricles was normal (– 3 ± 5°).

An abnormal RV was encountered in 106 patients (group II). The disease was considered diffuse in 30 cases and localized in 76 (1 segment was involved in 29 cases, 2 in 30, and 3 in 17) (Figure 4). Mean Fourier phase shift between ventricles was 72 ± 68° (P < 0.0001 versus group I). An LV abnormality was encountered in 14 patients, all in group II. Mean LVEF was 63 ± 9% in patients with normal LV and
45±11% in patients with abnormal LV (P<0.0001). In 4 cases, the LV wall motion abnormality was only regional, with LVEF 55%.

There was no difference in the clinical data between groups in terms of sex, age, and symptoms. The number of patients with abnormal resting ECG, positive SA-ECG, and inducible SVT was significantly higher in group II (Table 1).

**Follow-Up Data**

During follow-up, 84% of the patients were taking antiarrhythmic drugs, 16% underwent catheter ablation, 18 patients received an implantable cardioverter-defibrillator, and 3 patients underwent surgery. During this period, 14 patients experienced an SD episode; 3 of them were resuscitated. Their mean age (42.6±18 years old) was similar to that of survivors at the time of the RNA study; 8 patients initially presented with SVT, 5 with NSVT, and 1 with VPCs associated with syncope. Four patients had a normal ECG, and 6 had a normal SA-ECG. An interruption in antiarrhythmic therapy was confirmed in 7 patients, with the event occurring within 48 hours for 3 patients. In 1 patient, death occurred during sports competition. In 2 patients, SD followed heart failure.

No deaths occurred in group I patients (normal RNA study). Results of univariate analysis are described in Table 2 and show that 2 parameters were significant predictors of SD: the presence of an abnormal RNA and the presence of associated LV abnormalities. Figure 1 shows the high predictive value of an abnormal RNA study for survival (P<0.005).

There was no difference in rate of death between patients with diffuse (13.3%) or localized (13.2%) RV disease. The second scintigraphic parameter of high predictive value was the presence of LV abnormalities, either with global systolic dysfunction or even with limited wall motion abnormalities (Figure 2). The model selection procedure in the multivariate analysis identified an abnormal RNA study and LV abnormalities as independent predictors of SD (P<0.0001, likelihood ratio test). The adjusted hazard ratio for LV involvement was 4.95 (95% CI 1.50 to 1.74, P<0.008).

Clinical presentation, resting and stress ECG, Holter monitoring, SA-ECG (Figure 3), and EPS were not predictive of death. During follow-up, 43 patients had a recurrence of VT, 93% of which occurred despite therapy (13.4% in group I and 30.2% in group II; P<0.01). No clinical or ECG parameters were predictive of these recurrences. The only predictive factor was a positive RNA study, but it had a poor prognostic value (OR 2.8, 95% CI 1.3 to 6, P<0.01).

**Discussion**

In patients presenting with RV arrhythmias, the major goal of evaluation is the detection of individuals at risk for SD, which requires closer monitoring and therapeutic interventions.

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### TABLE 1. Patient Characteristics Classified by RNA Studies

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<tbody>
<tr>
<td>Group I (n=82)</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Syncope, %</td>
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<tr>
<td>SVT, %</td>
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<tr>
<td>Abnormal ECG, %</td>
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<td>Abnormal SA-ECG, %</td>
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<td>Positive Holter, %</td>
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<tr>
<td>Positive stress test, %</td>
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<tr>
<td>Positive EPS, %</td>
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<tr>
<td>Recurrence of VT, %</td>
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<td>Death or resuscitation, %</td>
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Values are mean (SD).

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### TABLE 2. Univariate Analysis of Factors Predicting Sudden Death

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<tbody>
<tr>
<td>No. of Patients</td>
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<tr>
<td>Presence of syncope</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Abnormal resting ECG</td>
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<td>Yes</td>
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<td>No</td>
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<td>Abnormal stress ECG</td>
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<td>Abnormal SA-ECG</td>
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<tr>
<td>Positive Holter</td>
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<td>No</td>
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<td>Positive EPS</td>
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<td>Yes</td>
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<td>No</td>
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<tr>
<td>Abnormal RNA</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Presence of LV involvement</td>
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<td>Yes</td>
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<td>No</td>
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Figure 1. Survival curve of patients considering results of RNA study. Group I patients had normal RNA, whereas group II patients presented with diffuse or localized RV abnormalities.
The major results of this study are the following: (1) patients presenting with RV arrhythmias but no apparent RV abnormalities on RNA are at very low risk of SD; (2) mortality remains high in patients with abnormal RV; (3) the detection of any type of RV abnormalities, even focal, by RNA is highly predictive of the risk of death, whereas none of the clinical or electrical data are predictive; and (4) the association of an LV abnormality with abnormal RV significantly increases the risk of death. These facts argue for a careful evaluation of both ventricles in this population, and in our experience, RNA may be used to perform such an evaluation accurately and noninvasively.

The long-term mortality of patients with RV arrhythmias has been studied extensively in the literature in the case of ARVC, ranging from 4% to 46% for similar follow-up duration. In our series, the global rate of SD for a mean follow-up of ≈4 years is 5.8% (7.4% including resuscitation cases). Considering patients with abnormal RV, it reached 10.4% and 13.2%. A therapeutic withdrawal was documented in half of these patients, sometimes after a very short interruption of 24 to 48 hours. This emphasizes the appeal of drugs with a long half-life and raises the question of indications for implantable cardioverter-defibrillators.

The cause of death in this population has been reported to be either heart failure or SD. In some series, heart failure was predominant or equally frequent. In the present study, probably because of an earlier diagnosis, all deaths were sudden, preceded by heart failure in only 2 cases.

The presence of structural or functional RV impairment is clearly a major factor underlying the risk of death. In the present study, all deaths occurred in the group with RV abnormalities, although the extent of these abnormalities was not predictive of death. This argues for careful, systematic detection of small RV abnormalities. X-ray angiography cannot be used as a screening tool, and reproducibility is not optimal. RNA, when performed in an appropriate way, has shown high diagnostic accuracy (93% compared with x-ray angiography) and reproducibility (96%). It is easy to perform and inexpensive. MRI is an emerging and promising tool that appears to be highly accurate when used by trained groups. On a routine basis, the best locally available noninvasive tool with sufficient sensitivity to detect localized biventricular abnormalities (MRI or RNA) should be used.

To define risk factors for death in ARVC, Peters and Reif compared 3 groups of patients (SVT, NSVT, or cardiac arrest and resuscitation). They found no difference in age, RV volume, RV and LV function, or RV structure at biopsy between groups. The rate of inducibility of SVT was also similar among patients with cardiac arrest or SVT. Segmental LV abnormalities without reduction in global LV function were present in 40% of the patients, without differences between groups.

In contrast, the involvement of the LV in the present series was the second risk factor that was predictive of death. This fact was previously reported in the study of Pinamonti et al. A recent article based on histopathological data reported LV involvement in 40% to 67% of cases. However, that series included only patients who died or underwent cardiac transplantation, which introduces a selection bias. In the present series, the majority of cases were less advanced forms, probably owing to earlier diagnosis. Moreover, the prevalence of LV involvement depends on the method of detection. Histopathological studies may catch nonclinical abnormal-
ties, and some patients with normal resting LV function may have abnormal LV function with exercise.9

Clinical and electrical study variables were not predictive of death in the present series. A history of syncpe had no prognostic value, in contrast with the report of Blomström-Lundqvist et al.19 The rate of ECG abnormalities (60% of patients with RV abnormalities in the present study, and 68% in the study of Berder et al25) is related to the extent of the disease at the time of the evaluation, and such abnormalities may appear during evolution of the disease.26 In addition, we found no prognostic value of inducibility of SVT by EPS, the presence of which seems correlated with the prevalence of spontaneous SVT.20,22

The same conclusion applies to the presence of late potentials at SA-ECG that have no predictive value for mortality. Although the prevalence of this condition is high (≈50% of the patients in all the studies), it is correlated with the extent of the disease, which is not predictive of SD.27–29

Limitations of the Study
To the best of our knowledge, this is the first large-scale report on prognostic factors of mortality in patients with RV arrhythmias. However, some limitations should be addressed. ARVC is a disease with a histopathological definition, and RNA only displays RV wall motion abnormalities. Thus, the diagnosis of ARVC can only be suggested by this technique; only an endomyocardial biopsy, rarely performed in France, could confirm it.

Twenty-six patients were lost to follow-up, with distribution similar to that of the overall population (12 in group I, 14 in group II). Mean follow-up duration was slightly shorter for group I patients (32.5 months) than for patients considered as having an ARVC (42.5 months).

Conclusions
The present study confirms that evidence of RV abnormalities, as detected by RNA, in patients presenting with RV arrhythmias is highly predictive for SD, as is an association with LV involvement. In contrast, clinical presentation, the presence of ECG or SA-ECG abnormalities, and the results of stress ECG, Holter monitoring, or programmed stimulation are not predictive for SD.

References
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