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CLINICAL PAPER

Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry

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Aims We sought to examine the clinical presentation and natural history and to identify long-term prognostic predictors in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) as information concerning the natural history and risk stratification of ARVC is still incomplete.

Methods and results A cohort of 96 ARVC patients (68% males, 35 ± 15 years) was enrolled and underwent structured diagnostic protocol and follow-up. Primary study endpoints were death and heart transplantation (HTx). Clinical and echo-Doppler data were assessed as prognostic indicators. Sixty-five per cent of patients had right ventricular (RV) systolic dysfunction (RV fractional area change < 33%) and 24% had left ventricular (LV) systolic dysfunction (LV ejection fraction <50%). During a mean follow-up of 128 ± 92 months, 20 patients (21%) experienced cardiac death or underwent HTx. At multivariate analysis (Model 1), RV dysfunction [hazard ratio (HR): 4.12; 95% confidence interval (CI): 1.01–18.0; $P = 0.05$], significant tricuspid regurgitation (HR: 7.6; 95% CI: 2.6–22.0; $P < 0.001$), and amiodarone treatment (HR: 3.4; 95% CI: 1.3–8.8; $P = 0.01$) resulted as predictors of death/HTx. When inserting in the model, the 'ordinal dysfunction' (Model 2), which considers the presence of both RV and LV dysfunctions, this variable emerged as an independent prognostic predictor (HR: 6.3; 95% CI: 2.17–17.45; $P < 0.001$). At the receiver operating characteristic analysis, Model 2 was significantly more accurate in predicting long-term outcome compared with Model 1 (area under the curve 0.84 vs. 0.78, respectively; $P = 0.04$).

Conclusion In our tertiary referral centre ARVC population, the presence of LV dysfunction at diagnosis has an incremental power in predicting adverse outcome compared with RV dysfunction alone.

Keywords Arrhythmogenic right ventricular cardiomyopathy • Heart failure • Left ventricular involvement • Arrhythmia

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), a primary myocardial disease that may lead to life-threatening ventricular arrhythmias and heart failure (HF), has a prevalence estimated between 1:2000 and 1:5000.[1,2] Arrhythmogenic right ventricular cardiomyopathy is a genetic disease,[3] and a familial trait has been reported in 30–50% of cases.[4,5]

Several desmosomal mutations[6,7] are considered to be responsible for the progressive loss of ventricular myocytes, and their replacement with fibro-adipose tissue, the pathologic landmark of the disease.

Originally, the structural abnormalities of ARVC were described in the right ventricle (RV). The consequent ventricular electric instability was considered the main clinical characteristic of the disease. However, left ventricular (LV) involvement in ARVC has

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also been reported,[8–12] and congestive HF can lead to death or heart transplantation (HTx).[1,2,9,13–15]

Although several studies[13–17] have been reported in patients with ARVC, they failed to provide consistent data regarding the natural history and risk stratification of the disease. Therefore, the aims of this study were to examine the clinical presentation and natural history of the disease, as well as to identify long-term prognostic predictors in a large cohort of patients with ARVC, specifically focusing on the prognostic impact of echocardiographic parameters and LV involvement.

Methods

Study population

Data were obtained from the Registry of Myocardial Diseases of Trieste where 98 patients with ARVC were enrolled between January 1976 and January 2008. All patients who met the ARVC diagnostic criteria[18] and with available follow-up (96 patients) were included in the present study. Family history, previous documented ventricular arrhythmias, age, and symptoms at onset were systematically assessed. All patients underwent clinical examination, 12-lead electrocardiogram (ECG), and echocardiography (M-mode measurements since 1976, two-dimensional since 1982, and Doppler and colour-Doppler since 1986). Signal-averaged ECG, 24 h Holter monitoring, exercise stress test, magnetic resonance imaging, coronary angiography, haemodynamic study, and endomyocardial biopsy were performed in selected cases, according to clinical indications.

Patients were treated for arrhythmias and HF. Anti-arrhythmic drug treatment was prescribed for frequent and repetitive ventricular arrhythmias, regardless of the presence of related symptoms. Implantable cardioverter-defibrillator (ICD) devices were implanted according to clinical indications.[19] Patients with HF were treated with diuretics and digitalis, and since 1988 also with angiotensin-converting enzyme (ACE)-inhibitors. In selected cases, beta-blockers were used.

Available data were obtained retrospectively in the patients with an ARVC diagnosis before 1993; subsequently, data acquisition and analysis were made in a prospective manner. Only baseline clinical and laboratory data were considered in the present study.

Study design

A primary endpoint was cardiovascular death or HTx. The cause of cardiovascular death was based on a clinical history of sudden death (SD) or death due to refractory HF. Sudden death was defined as an immediate death or occurring within 1 h after the onset of symptoms or during sleep in stable New York Heart Association (NYHA) I–III functional class patients. Patients who suffered a non-cardiac death were censored, whereas a death of unknown cause was considered a primary endpoint, preferring to obtain a less conservative estimate than to run the opposite risk. The end of follow-up was the last available clinical visit or the date of death or HTx. Endpoint data were obtained directly from patients during periodic evaluations, from patients' physician or relatives, or from the death registry of the patients' municipality. The disease was considered familial if there was clinical or post-mortem diagnosis of ARVC or SD at young age (<35 years) in a first-degree relative. ARVC patients were distinguished into probands (the first diagnosed case in an affected family) and family members.

Right ventricular systolic dysfunction was defined by two-dimensional echocardiography: an RV fractional area change (FAC; from apical four-chamber view) <33% (<2 standard deviations from normal values) defines RV systolic dysfunction, while RV FAC $\leq$ 25% ($\leq$3 standard deviations from normal values) defines severe RV systolic dysfunction.[20] Left ventricular systolic dysfunction was defined as an LV ejection fraction (EF; obtained by the biplane Simpson's method) < 50%; it was classified as mild (LVEF: 45–49%), moderate (LVEF: 36–44%), or severe (LVEF $\leq$ 35%). Right ventricle and LV were considered as enlarged when RV end-diastolic area > 24 cm^2 and indexed LV end-diastolic volume > 76 mL/m^2.[21]

We defined 'ordinal dysfunction' to arbitrarily classify the presence of ventricular dysfunction into three stages: 0 = no ventricular dysfunction, 1 = presence of RV dysfunction, and 2 = biventricular dysfunction. In patients with available colour-Doppler data, assessment of mitral regurgitation (MR) and tricuspid regurgitation (TR) was made semi-quantitatively, according to international guidelines.[22] For the purpose of the analysis, MR and TR were considered as significant in the presence of a regurgitant jet area >4 cm^2 on colour-Doppler.

Statistical analysis

Summary statistics of clinical and instrumental variables at enrolment were expressed as a mean and standard deviation or a count and percentage, as appropriate. Comparison between patients with and without events was made by the ANOVA test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold, and the χ^2 test for discrete variables. Survival curves were calculated by using the Kaplan–Meier method for the entire population and then stratified by the level of dysfunction; the comparison between the estimated curves was performed with the log-rank test. Univariate Cox proportional hazards models were applied to find predictors of primary endpoints. Multivariable Cox models were then estimated to determine the relationship between a subset of baseline clinical-laboratory characteristics and the long-term outcome. In particular, we compared the additive prognostic power of two different models. Model 1 included clinical as well as echo-Doppler data of the right heart, whereas in Model 2 the 'ordinal dysfunction' was inserted, thus including LV dysfunction. The covariates were selected from univariate analysis and by taking into account the limited number of events by means of a backward-conditional step-wise procedure. Subjects with missing data in the selected covariates were deleted case-wise. Areas the under receiver operating characteristic (ROC) curve of the estimated cumulative hazard functions were compared to check a possible increase in predictive accuracy of the estimated Cox models. The results were considered statistically significant with $P < 0.05$.

Inter- and intra-observer variability regarding RV areas and FAC was verified by selecting a sample size of 30 ARVC patients (four observations per subject: two different operators, double evaluation each) to achieve 90% power and, thus, to detect an intra-class correlation (ICC) of 0.8 under the null hypothesis of ICC = 0.5, by using an *F*-test, with a significance level of 0.05.[23] The intra-observer variability was evaluated by computing the paired correlation between repeated measures of the same operator. For all the evaluated parameters the ICC values were $\geq$0.95 and paired correlations were $\geq$0.90. Statistical analyses were performed with SPSS Statistical Package 14.0 and *R* statistical software (version 2.7.2).

Results

The study population counted 96 patients of whom 76 (79%) were probands and 20 (21%) were family members.

The clinical and laboratory findings of the patients are summarized in *Tables 1* and *2*, with the frequency of major and minor

Table 1 Clinical and laboratory data of arrhythmogenic right ventricular cardiomyopathy patients at baseline, classified according to primary endpoint at follow-up: Group A: patients with events during follow-up (cardiovascular death or heart transplantation); Group B: surviving patients

	Global population ($n = 98$)	Group A patients ($n = 20$)	Group B patients ($n = 78$)	*P*-value
Clinical history/physical examination				
Males (%)	68	60	69	NS
Age at diagnosis (years)	34 ± 15	35 ± 17	34 ± 15	NS*
Probands (%)	79	70	80	NS
Family history (%)[a]	46	65	40	0.04
Sudden death [<35 years, (%)][a]	33	39	31	NS
Clinical diagnosis (%)[a]	52	46	55	NS
Confirmed by autopsy (%)[b]	14	15	14	NS
Duration of symptoms (months)	47 ± 59	44 ± 56	48 ± 60	NS
Asymptomatic (%)	27	20	29	NS
Palpitations (%)	41	25	45	NS
Syncope (%)	15	0	19	0.04
Chest pain (%)	4	5	4	NS
Cardiac arrest (%)	3	0	4	NS
Heart failure symptoms (%)	17	35	12	0.02
NYHA III–IV (%)	5	15	3	0.03
ECG				
Abnormal ECG (%)	78	90	75	NS
Low-voltage QRS (%)	16	30	11	0.05
Complete RBBB (%)	4	10	3	NS
Epsilon waves (%)[b]	16	35	11	0.007
Localized QRS dispersion [>110 ms in right precordial leads, (%)][b]	5	5	5	NS
Negative anterior T-waves (%)[a]	51	70	46	NS
SVT at presentation (%)	23	35	20	NS
SVT LBBB pattern (%)[a]	19	20	19	NS
Atrial fibrillation/flutter	4	10	3	NS
SAECG (in 39% of pts)				
Late potentials (%)[a]	62	60	63	NS
Holter registration (in 65% of pts)				
PVB>1000/24 h[a]	48	64	43	NS
Couples (%)	52	71	46	NS
NSVT LBBB pattern (%)[a]	34	50	30	NS
Supraventricular arrhythmias (%)	19	21	18	NS
Exercise test (in 67% of pts)				
Functional capacity (W)	138 ± 56	101 ± 47	145 ± 56	NS
Interruption for arrhythmias (%)	9	9	9	NS
Exercise SVT LBBB pattern (%)[a]	5	9	4	NS
Exercise frequent PVB (%)	37	64	32	0.04
Electrophysiological study (in 27% of pts)				
Induced MVA (%)	50	20	57	NS
LBBB morphology of induced MVA (%)	62	0	67	NS

Continued

Table I *Continued*

	Global population ($n = 98$)	Group A patients ($n = 20$)	Group B patients ($n = 78$)	*P*-value
Cardiac catheterization (in 41% of pts)				
Right atrial pressure (mmHg)	4 ± 3	4 ± 4	4 ± 3	NS
Pulmonary artery systolic pressure (mmHg)	22 ± 7	23 ± 7	21 ± 7	NS
Pulmonary capillary pressure (mmHg)	8 ± 3	8 ± 4	8 ± 3	NS
Mean aortic pressure (mmHg)	87 ± 17	84 ± 25	88 ± 14	NS
Cardiac index (L/min/m^2)	3.7 ± 1.1	3.5 ± 1.4	3.7 ± 1.0	NS
Magnetic resonance (in 21% of pts)				
RV fat tissue (%)	50	50	50	NS
RV aneurysm (%)	38	100	29	0.05
LV fat tissue (%)	15	50	11	NS
Right ventricular biopsy (in 26% of pts)				
RV fibro-fatty infiltration (%)[b]	52	50	53	NS
Treatment				
Anti-arrhythmics (%)	58	75	54	NS
Amiodarone (%)	24	50	17	0.002
Sotalol (%)	19	15	20	NS
Beta-blockers [except sotalol, (%)]	20	15	21	NS
ACE-inhibitors (%)	17	30	13	NS
Digitalis (%)	15	45	7	0.001
Vasodilators (%)	12	30	7	0.03
Diuretics (%)	17	60	5	0.001

MVA, major ventricular arrhythmia; LBBB, left bundle branch block; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; pts, patients; PVB, premature ventricular beats; RBBB, right bundle branch block; RV, right ventricular; SAECG, signal-averaged electrocardiogram; SVT, sustained ventricular tachycardia.
[a]Minor diagnostic criteria.
[b]Major diagnostic criteria.
*Brown–Forsythe statistic.

criteria for ARVC diagnosis.[18] In the tables, the study population was classified in two subgroups according to the presence (Group A) or the absence (Group B) of primary endpoints during follow-up.

Approximately one-third of the patients (27%) were diagnosed during an asymptomatic phase (family screening or abnormal ECG). The most frequent clinical presentation was related to arrhythmias [palpitations (41%), syncope (15%), and cardiac arrest (3%)], followed by HF symptoms (17%). An advanced NYHA class was present in a minority of cases (5%).

ECG abnormalities were frequent (78%), most commonly characterized by negative anterior T-waves (51%). Ventricular arrhythmias (documented on ECG during the episode or on Holter monitoring) were frequent (61 patients; 61%), characterized by predominant left bundle branch block pattern: sustained ventricular tachycardia (VT) in 23%, non-sustained VT in 34%, and frequent ventricular ectopic beats in 48%. Supraventricular arrhythmias were documented in 19% (atrial fibrillation in 4%).

On two-dimensional echocardiography (available in 92 patients), RV abnormalities were present in all of them, characterized by RV hypokinesis (92%), and RV aneurysms (71%), mainly located at subtricuspid (43%) and apical (39%) areas. Right ventricular enlargement and systolic dysfunction were present in 79 and 64% of patients, respectively.

Left ventricular involvement was present in 45 patients and was characterized by the following: LV wall motion abnormalities (45%), LV systolic dysfunction (26%), and LV dilatation (14%). Left ventricular aneurysms were found in only two cases, both located at the apex. Significant MR was found in 2 of 84 patients studied with Doppler (3%), and significant TR in 14 of 84 (15%). Intra-cardiac thrombi were observed in two patients, one located within the right atrium and the other at the RV apex.

Probands, with respect to family members, were more symptomatic and more frequently presenting with HF.

Endpoint data

During a mean follow-up of 128 ± 92 months (median = 120 months), 20 patients reached a primary endpoint (Group A): 12 of them died of cardiac cause (SD: six patients, refractory HF: six patients), one died of unknown causes (included in group A, see methods), and seven underwent HTx. Two patients died of a non-cardiac cause (neoplasm), and were censored.

Twelve patients received an ICD [nine for secondary prevention following aborted SD (one patient) or sustained VT (eight patients)

Table 2 Echocardiographic parameters of arrhythmogenic right ventricular cardiomyopathy patients classified according to primary endpoint at follow-up

	No. of patients with available data	Global population ($n = 96$)	Group A patients ($n = 20$)	Group B patients ($n = 76$)	*P*-value
Right heart					
RVEDAI (cm^2/m^2)	92	17 ± 5	18 ± 6	16 ± 4	NS
RV dilation [RVEDA >24 cm^2, (%)][a]	92	79	78	79	NS
RV FAC (%)	92	29 ± 12	23 ± 11	30 ± 12	0.03
RV dysfunction [FAC $<33\%$, (%)][a]	92	64	90	58	0.01
Severe RV dysfunction [FAC $<26\%$, (%)][b]	92	46	74	38	0.006
RV aneurysms (%)[b]	92	71	65	72	NS
Regional RV hypokinesia (%)[a]	92	92	90	93	NS
RAAI (cm^2/m^2)	92	12 ± 6	18 ± 8	11 ± 5	0.003
Significant tricuspid regurgitation (%)	84	15	35	9	0.004
Left heart					
LVEDDI (mm/m^2)	96	29 ± 4	30 ± 4	29 ± 4	NS
LVESDI (mm/m^2)	96	20 ± 5	22 ± 6	19 ± 4	0.04*
LV dilation (%) (LVEDVI >76 mL/m^2)	92	14	20	13	NS
LVEDVI (mL/m^2)	92	56 ± 19	56 ± 24	56 ± 18	NS*
LVESVI (mL/m^2)	92	26 ± 14	31 ± 20	25 ± 12	NS*
LVEF (%)	92	56 ± 12	47 ± 12	58 ± 11	0.001
LV dysfunction (%)	92	26	47	20	0.01
Mild LV dysfunction (%)	92	9	15	8	NS
Moderate LV dysfunction (%)	92	9	10	9	NS
Severe LV dysfunction (%)	92	6	20	3	0.004
LV wall motion abnormalities (%)	92	45	65	40	0.04
LV aneurysms (%)	92	2	5	1	NS
LADI (mm/m^2)	96	19 ± 3	20 ± 3	18 ± 3	0.003
LAAI (cm^2/m^2)	92	11 ± 3	12 ± 5	11 ± 2	NS*
Significant mitral regurgitation (%)	84	3	0	4	NS

FAC, fractional area change; LAAI, left atrial area indexed; LADI, left atrial diameter indexed; LV, left ventricular; LVEDDI, left end-diastolic diameter indexed; LVEF, left ventricle ejection fraction; LVESDI, left end-systolic diameter indexed; LVEDVI, left end-diastolic volume indexed; LVESVI, left end-systolic volume indexed; RAAI, right atrial area indexed; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVEDAI, right ventricular end-diastolic area indexed.
[a]Minor diagnostic criteria.
[b]Major diagnostic criteria.
*Brown–Forsythe statistic.

and three for primary prevention of SD]. Appropriate ICD interventions (for sustained VT) were observed in 3 of 12 implanted patients (25%). No aborted SD was observed during follow-up in any patient.

The long-term outcome of the whole population with ARVC is illustrated in *Figure 1*. Event-free-survival from cardiac death or HTx at 2, 5, and 10 years was 96, 87, and 79%, respectively.

The variables associated with worse prognosis at univariate analysis are shown in *Table 3*.

Group A patients had a more severe clinical presentation, characterized by a higher frequency of HF and advanced NYHA class as well as higher percentage of epsilon waves on ECG with respect to Group B patients; in addition, they were treated more frequently with amiodarone and HF drugs. At echocardiography, patients of Group A had more frequently RV as well as LV systolic dysfunctions, atrial enlargement, and significant TR on colour-Doppler.

A progressive increase of mortality and HTx rate ($P = 0.003$) was observed in the presence of RV and biventricular dysfunction, respectively (*Figure 2*).

On Cox multivariate analysis, considering Model 1 (*Table 4*), the three significant independent predictors of death/HTx were: significant TR [hazard ratio (HR): 7.6; 95% confidence interval (CI): 2.6–22.0; $P < 0.001$], RV dysfunction (HR: 4.12; 95% CI: 1.01–18.0; $P = 0.05$), and amiodarone treatment (HR 3.4; 95% CI: 1.3–8.8; $P = 0.01$).

In Model 2 (*Table 5*), ordinal dysfunction was found to be a powerful predictor of death/HTx (HR: 6.3; 95% CI: 2.17–17.45; $P < 0.001$), along with significant TR and amiodarone treatment.

The incremental prognostic accuracy of Model 2 compared with Model 1 was shown by comparing the ROC curves (area under the

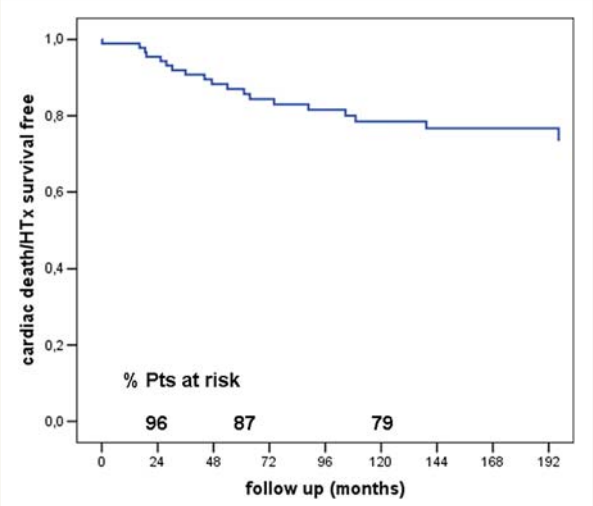

Figure 1 Kaplan–Meier curve for cardiac death or transplant-free survival of arrhythmogenic right ventricular cardiomyopathy population (cumulative proportion of surviving patients with arrhythmogenic right ventricular cardiomyopathy from diagnosis to cardiac death or heart transplantation). D/HTx, cardiac death/heart transplantation; Pts, patients.

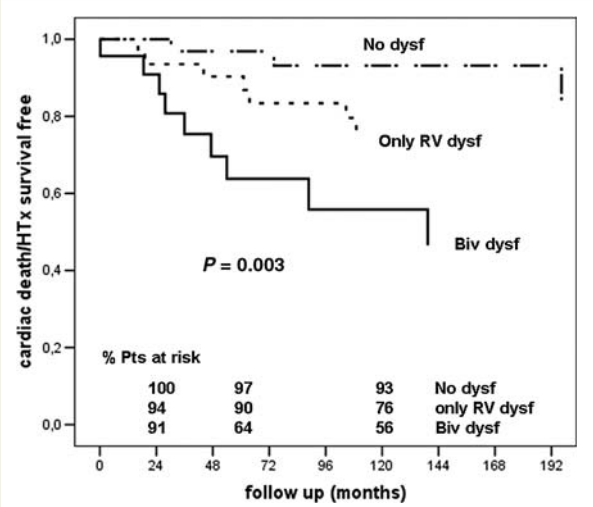

Figure 2 Kaplan–Meier survival curves of arrhythmogenic right ventricular cardiomyopathy patients classified according to the 'ordinal ventricular dysfunction' (dashed line = no ventricular dysfunction; dotted line = right ventricular dysfunction; solid line = biventricular dysfunction). Cardiac death or transplant-free-survival significantly decreased with increasing the ventricular dysfunction score. D/HTx, cardiac death/heart transplantation; dysf, dysfunction; Pts, patients, RV, right ventricular.

Table 3 Clinical and laboratory variables associated with cardiovascular death/HTx at univariate analysis

	HR	95% CI	*P*-value
Ordinal dysfunction[a]	2.50	1.52–4.09	<0.001
NYHA III–IV	8.15	2.18–30.53	0.002
Heart failure symptoms	3.90	1.54–9.87	0.004
Epsilon wave	4.03	1.59–10.27	0.003
LVEF (%)	0.93	0.89–0.96	<0.001
LV dysfunction	3.92	1.57–9.78	0.003
Severe LV dysfunction	5.67	1.81–17.75	0.003
LADI (mm/m^2)	5.23	1.43–19.3	0.01
RVFAC (%)	0.95	0.91–0.99	0.02
RV dysfunction	5.48	1.27–23.74	0.02
Severe RV dysfunction	4.93	1.72–14.12	0.003
Significant TR	5.59	2.17–14.41	<0.001
ACE-inhibitors	3.16	1.18–8.43	0.02
Digitalis	5.79	2.38–14.00	<0.001
Diuretics	14.27	5.59–36.43	<0.001
Amiodarone	3.46	1.42–8.38	0.006

CI, confidence interval; FAC, fractional area change; HR, hazard ratio; HTx, heart transplantation; LADI, left atrial diameter indexed; LV, left ventricular; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association functional class; RV, right ventricular.
[a]Ordinal dysfunction: 0, no systolic ventricular dysfunction; 1, RV dysfunction; 2, biventricular dysfunction (see text).

curve 0.84 vs. 0.78, respectively; $P = 0.04$; *Figure 3*). No significant difference in terms of transplant-free-survival between probands and familial cases was observed.

Table 4 Independent predictors for cardiac death/heart transplantation (Model 1)

Model 1	HR	95% CI	*P*-value	AUC
Significant tricuspid regurgitation	7.60	2.60–22.0	<0.001	0.78
Amiodarone	3.40	1.30–8.80	0.01	
Right ventricular dysfunction	4.12	1.0–18.0	0.05	

AUC, area under the curve; CI, confidence interval; HR, hazard ratio.

Discussion

We analysed a large cohort of patients, consecutively enrolled in the last 30 years in a tertiary referral centre for the study of HF and cardiomyopathies. Our results permitted a comparison of the presentation and the clinical-laboratory characteristics of ARVC patients with those of previous studies.[1,9,11–14] Furthermore, the natural history of the disease was observed, and early prognostic stratification models were defined.

Clinical and laboratory characteristics at the time of enrolment

This study supports some clinical and laboratory features of ARVC that already emerged from previous studies.[11–13] The disease has a considerable variability of clinical presentation.[1,2,4,5,9,10,14,15,24] A familial pattern was found in approximately half of the cases.

Table 5 Independent predictors for cardiac death/ heart transplantation (Model 2)

Model 2	HR	95% CI	*P*-value	AUC
Significant tricuspid regurgitation	5.09	1.86–13.93	<0.001	0.84
Amiodarone	3.72	1.43–9.67	0.007	
Ordinal ventricular dysfunction[a]	6.30	2.17–17.45	<0.001	

AUC, area under the curve; CI, confidence interval; HR, hazard ratio.
[a]Ordinal ventricular dysfunction: 0, no ventricular dysfunction; 1, RV dysfunction; 2, biventricular dysfunction.

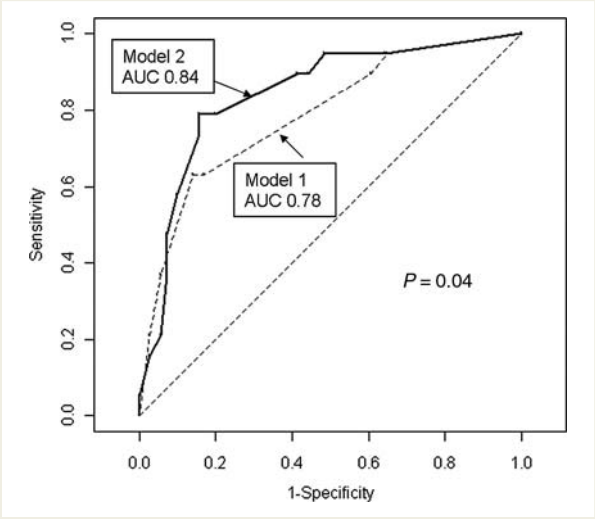

Figure 3 Comparison of the predictive accuracies between Model 1 and Model 2. The area under the curve of receiver operating curve of Model 2 incorporating the ordinal ventricular dysfunction score was significantly higher with respect to that of Model 1 (see text for explanation). AUC, area under the curve.

This percentage is higher than previously reported[4,14,15] and is probably the result of systematic family screening.

Together with RV dysfunction, our echocardiographic data showed a frequent LV involvement. This finding, previously described by our group,[8] was also confirmed in other study populations.[10–16] Most recently, Sen-Chowdhry *et al.*[11] defined a new nosological entity within the ARVC group known as 'left-dominant arrhythmogenic cardiomyopathy' with prevalent or even exclusive LV involvement. The high proportion of LV involvement in our population could reflect an advanced disease stage typical of patient selection due to referral to a Cardiomyopathy service.

Natural history and prognosis

In our population, the overall mortality was 15% during a median 10-year follow-up. The incidence of cardiovascular deaths plus HTx was ~1.9/100 patients per year, similar to that reported by Hulot *et al.*[14] but higher than that found by Nava *et al.*[17] This difference may be explained by the fact that our population comes from a tertiary centre where patients are frequently referred for advanced cardiac failure.

Role of biventricular involvement in prognostic stratification

The presence of RV dysfunction at diagnosis was found to be an independent predictor of death/HTx. Hulot *et al.*[14] were the first to describe a worse prognosis in patients with RV dysfunction. Our study emphasizes that long-term outcome is influenced not only by the presence of RV dysfunction, a classical abnormality found in ARVC, but also by LV dysfunction, as observed by others.[14,16] Furthermore, we clearly demonstrate the incremental prognostic value of LV dysfunction in the risk stratification of patients affected by ARVC.

Possible mechanisms by which right ventricular and left ventricular dysfunction may increase the risk of life-threatening arrhythmias and heart failure

Major arrhythmic events and SD can occur in both early and advanced stages of disease, albeit due to presumably different mechanisms. In the so-called 'concealed' phase, characterized by little or no evidence of heart disease; it was hypothesized that gap junction remodelling[25] may account for the high arrhythmogenicity in the absence of ventricular structural abnormalities.

Subsequently, in the overt stage of disease, the fibro-fatty replacement of the myocardium can favour re-entry circuits leading to potentially life-threatening arrhythmias. The progressive myocyte loss and replacement with fibro-fatty tissue, due to intrinsic genetically determined structural pathology and stress, are also responsible for the gradual dilation and functional RV and LV impairment that eventually result in progressive HF.

Potential adverse prognostic significance of amiodarone treatment

In our study, anti-arrhythmic treatment with amiodarone was found to be an independent predictor of mortality.

This finding seems in contrast to the results of a recent study by Marcus *et al.*[26] where amiodarone emerged as protective against VT in ARVC; however, in comparison with ours, in the above-mentioned study the length of follow-up was too short (1.3 ± 1.1 years) to evaluate the long-term effect of amiodarone and the potential impact of widely known, time-related adverse effects of this particular treatment.[27]

Most importantly, in our study, amiodarone was indicated for the secondary prevention of life-threatening arrhythmias in selected, relatively young patients. Thus, it is possible that amiodarone treatment could be selected as a predictor of poor outcome as a proxy of the complex arrhythmic burden, which indicated its administration. This was especially true in the case of patients with highly arrhythmogenic phenotype who were enrolled before the demonstration of efficacy of ICD and for whom amiodarone was the only valid anti-arrhythmic option. Furthermore, our findings

underline the increasing need for appropriate selection of the ARVC patients who could benefit most by an ICD implantation in the long term.

Role of significant tricuspid regurgitation

To our knowledge, our study is the first to demonstrate an adverse prognostic impact of significant TR in ARVC. Tricuspid regurgitation, in patients with dilated and dysfunctioning RV, as in the case of MR in dilated cardiomyopathy, is usually functional and secondary to RV and right atrial remodelling and it may contribute to the worsening of HF by both increasing RV filling pressure and lowering RV forward stroke volume.

Study limitations

In the present study, RV size and systolic function were assessed by measuring two-dimensional echocardiography RV areas and FAC. This method, although correlated with RV volumes and EF,[21] is potentially inaccurate due to the complex geometry of this chamber. The recent advent of three-dimensional echocardiography, which correlates favourably with magnetic resonance,[28,29] may overcome this limitation and be employed in future studies with ARVC. Genetic characterization was not available in the majority of our study patients. Therefore, potential differences in clinical spectrum and prognostic impact of different genetic substrates cannot be ascertained.[10] Furthermore, since our patient population with ARVC comes from a tertiary centre where patients are frequently referred for advanced HF and complex diseases, they probably do not represent an unselected ARVC population. In addition, in the present study, we analysed only clinical and laboratory data at enrolment. Since the true onset of the disease in the single patient is unknown, our evaluation was performed at different stages of the disease in different patients. In this respect, an extensive follow-up study to assess the progression of clinical and echo-Doppler RV and LV dysfunctions and their possible prognostic role is advisable.[13]

In our population, cardiac arrest represented the first manifestation of the disease in three patients. Only one of these patients was subsequently implanted with an ICD. The remaining two patients were diagnosed in the early 1990s when ICD was not yet available. They remained stable in anti-arrhythmic treatment, and therefore, a conservative approach was chosen. None of our patients experienced an aborted SD during the follow-up period, and appropriate ICD interventions were due to VT without cardiac arrest. Therefore, these patients were not included in Group A.

After the initial submission of this paper, revised diagnostic criteria of ARVC were published.[30] Our patients were diagnosed using the traditional criteria; however, the diagnosis of ARVC was confirmed by testing the new criteria in all patients.

Conclusions

Arrhythmogenic right ventricular cardiomyopathy is characterized by a variable clinical presentation. In addition to electrical instability, in a selected patient population with advanced disease, HF and LV involvement appear to be common features of the disease. Their assessment at the time of presentation can provide prognostic stratification of patients. The main independent long-term predictors of death or HTx that emerged from our data were RV dysfunction, significant TR, biventricular involvement, and amiodarone treatment.

Therefore, a prognostic stratification that considers not only the presence of RV dysfunction but also LV dysfunction increases the power of the prognostic model. The finding that amiodarone therapy is associated with a poor long-term outcome suggests the presence of an electrical instability resistant to first-line anti-arrhythmic treatment and, thus, characterized by an intrinsic malignancy.

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