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Histologic Findings in Patients With Clinical and Instrumental Diagnosis of Sporadic Arrhythmogenic Right Ventricular Dysplasia

Cristina Chimenti, MD, PHD,* Maurizio Pieroni, MD,* Attilio Maseri, MD,* Andrea Frustaci, MD†
Milan and Rome, Italy

OBJECTIVES We sought to analyze the histologic findings of 30 patients with a diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) based on established clinical and instrumental criteria, who did not have a family history of ARVD.

BACKGROUND The diagnostic role of endomyocardial biopsy (EMB) in patients with a clinical profile of ARVD is still debated.

METHODS Thirty patients (19 male, 11 female, mean age 27 ± 10 years) with left bundle branch block morphology ventricular tachyarrhythmias and echocardiographic, angiographic, and magnetic resonance imaging (MRI) findings diagnostic of ARVD were studied. All patients, besides diagnostic, noninvasive, and invasive cardiac studies, underwent EMB in the apex, anterior free wall, inferior wall of the right ventricle (RV) and in the septal-apical region of the left ventricle.

RESULTS Diagnostic histologic features of ARVD were found only in 9 (30%) patients and a myocarditis, according to the Dallas criteria, in the remaining 21 (70%) patients. Morphometric evaluation of RV samples showed significant differences in fatty tissue and myocyte percent area between ARVD and myocarditis ($p < 0.001$). Conversely, no difference was found between the two groups in arrhythmic patterns and structural and functional echocardiographic, angiographic, and MRI RV alterations. Magnetic resonance imaging showed hyperintense signals in 67% of ARVD and in 62% of myocarditis group (p = NS). During follow-up (mean, 23 ± 14 months), all patients with myocarditis remained stable on antiarrhythmic therapy while five patients with ARVD required implantation of an implantable cardioverter defibrillator.

CONCLUSIONS A myocarditis involving the RV can mimic ARVD. An EMB appears the most reliable diagnostic technique, with significant prognostic and therapeutic implications. (J Am Coll Cardiol 2004;43:2305–13) © 2004 by the American College of Cardiology Foundation

The occurrence of ventricular tachyarrhythmias with left bundle branch block morphology, particularly in the presence of echocardiographic, angiographic, and magnetic resonance imaging (MRI) abnormalities confined to the right ventricle (RV), suggests a diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) (1,2).

Standardized diagnostic criteria for this disease have been defined (3), but their value in distinguishing sporadic cases of ARVD from other arrhythmogenic cardiac diseases, involving selectively the RV, is still unclear.

We report the histologic findings of biventricular biopsies performed in a series of 30 patients in whom the clinical diagnosis of sporadic ARVD was made on accepted standard clinical and instrumental criteria.

METHODS

Patient selection and clinical studies. Among 78 consecutive patients (43 male, 35 female, mean age 38 ± 17 years) with ventricular tachyarrhythmias, normal left ventricular (LV) global function, and normal coronary arteries hospitalized at our institution from 1998 to 2001, 30 (19 male, 11 female, mean age 27 ± 10 years) had tachyarrhythmias with left bundle branch block morphology associated with RV morphologic and functional alterations. All patients were submitted to noninvasive cardiac studies including resting electrocardiogram (ECG), signal-averaged ECG, Holter monitoring, ECG stress test, two-dimensional Doppler echocardiography, and cardiac MRI by ECG-triggered multislice spin-echo sequence and cine imaging with intravenously administered gadolinium.

To investigate possible occurrence of familial cardiomyopathies, ECG and echocardiographic studies were also extended to first-degree family members. Invasive studies were performed in all patients after informed consent and approval by the ethical committee of our institution. These studies included: electrophysiologic study according to the American College of Cardiology/American Heart Association guidelines (class I indication), cardiac catheterization, coronary angiography, right biplane ventriculography (30° right anterior oblique and 60° left anterior oblique), left ventriculography, and biventricular endomyocardial biopsy (EMB).

Biopsies were performed by a Bipal (Cordis, Miami, Florida) bioptome, approached by a 7F (501-613 and 501-613A) long sheet both in the septal-apical region of the RV and in specific areas with wall motion abnormalities

From the *Cardio-Thoracic and Vascular Department, San Raffaele Hospital, Milan, Italy; and the †Cardiology Department, Catholic University, Rome, Italy. Partially supported by the grant "Sudden Death in Young People" from the Italian Ministry of Health, Italy.

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Abbreviations and Acronyms

ARVD = arrhythmogenic right ventricular dysplasia
EMB = endomyocardial biopsy
HPF = high-power field
ICD = implantable cardioverter defibrillator
LV = left ventricle/ventricular
MRI = magnetic resonance imaging
nsVT = nonsustained ventricular tachycardia
PVB = premature ventricular beats
RV = right ventricle/ventricular
sVT = sustained ventricular tachycardia

(i.e., apex, anterior free wall, inferior wall) (four to five samples per patient) and in the septal-apical region of the LV (two to three specimens per patient). The regions candidate for a biopsy were identified on an X-ray view using flashing of contrast medium. The tissue specimens were fixed in 10% buffered formalin and embedded in paraffin wax for histologic studies or snap frozen in OCT compound with isopentane cooled in liquid nitrogen and stored at −80°C for molecular biology studies.

Histologic studies. Six to eight endomyocardial samples (2 to 3 mm in depth, 3 to 4 mm in length) obtained from each patient were processed for histologic and immunohistochemical studies. For histology, multiple 5-μm thick sections were cut and stained with hematoxylin-eosin, Miller's elastic Van Gieson, Masson's trichrome, and examined by light microscopy. The Dallas criteria (4) were followed for histologic diagnosis of myocarditis. Immunohistochemistry for the characterization of inflammatory infiltrate was carried out by using the following antibodies: CD45 (Dako [Carpinteria, California] 1:20), CD43 (Dako 1:40), CD45RO (Dako 1:100), CD20 (Dako 1:100), CD68 (Dako 1:50), CD3 (Dako 1:50), CD4 (Novocastra [New Castle, United Kingdom] 1:50), CD8 (Dako 1:100), as already described (5). These antibodies recognize cluster of differentiation molecules specific for different classes of lymphocytes. Briefly, after deparaffination, the sections were incubated with the monoclonal antibody for 1 h at room temperature and were then incubated with biotinylated antimouse immunoglobulins (Dako EnVision Peroxidase Mouse) for 30 min. Enzyme activity was detected with diaminobenzidine (0.5 mg/ml) with 0.05% NiCl in 50 mmol/l Tris buffer, pH 7.5, and sections were counterstained with Mayer's hematoxylin.

To quantify the inflammatory infiltrates, CD45 positive leukocytes and T-lymphocytes (CD3+) were counted per high-power field (HPF) (400-fold magnification) in all available fields, and the mean number was calculated, as previously described (6). More than 2.0 CD3-positive lymphocytes per HPF (7 per mm^2) were considered as abnormal (6). The presence of an inflammatory infiltrate of a minimum of 14 infiltrating leukocytes/mm^2 was considered diagnostic for myocarditis (7).

For morphometric analysis, RV histologic sections were examined at 400× magnification with a reticule containing 42 sampling points (105844, Wild Heerbrugg Instruments, Gals, Switzerland) (8). This reticule was used to determine the percent area occupied by myocytes, fibrous tissue, adipose tissue, and other components (vascular spaces, interstitial cells). Control RV biopsies (two to three per patient) for quantitative evaluation of inflammatory infiltrates and for morphometry were obtained from 15 age-matched patients (26 ± 12 years) at the time of a surgery for atrial septal defect repair. These control surgical endomyocardial biopsies were collected in the setting of a pathologic study approved by our ethical committee.

Because of the young age of the patients, a percentage of fatty tissue >3.5% was considered diagnostic of ARVD (9). In fact, an increased amount of fatty tissue has been shown in the heart of elderly (10) compared with the heart of youth, where the adipose tissue is virtually absent (11).

Molecular biology studies. Two frozen myocardial specimens per patient were used to assess the presence of cardiotropic viruses (adenovirus, enterovirus, cytomegalovirus, parvovirus B19, influenza A and B viruses, herpes simplex viruses, Epstein Barr virus, hepatitis C virus); PCR and RT-PCR analysis was performed as previously described (5). Frozen endomyocardial samples from five age-matched patients with chronic stable angina, no systemic infection, no history of myocarditis, and no histologic evidence of cardiac inflammation were used as controls. In four cases, the biopsies were surgical samples taken at the time of bypass surgery: two patients (25 and 29 years) were affected by familiar hypercholesterolemia and had multiple coronary stenosis, two patients (43 and 39 years) were affected by a coronary stenosis involving only the left anterior descending artery. The other control biopsies were endomyocardial specimens from a patient (33 years) affected clinically by chronic stable angina in absence of coronary artery stenosis (syndrome X). The biopsies were performed both in the RV and in the LV and were obtained from different regions (two to three samples per each patient). The indication for this procedure was to study the intramyocardial small vessels in a research project approved by our ethical committee.

Treatment and follow-up. Patients with frequent and complex premature ventricular beats (PVB) and with nonsustained ventricular tachycardia (nsVT) were treated with sotalol or beta-blockers.

Patients with sustained ventricular tachycardia (sVT) were treated according to the results of electrophysiologic serial drug testing. An implantable cardioverter defibrillator (ICD) was implanted in inducible or spontaneous ventricular tachycardia resistant to drug therapy (presence of sVT in spite of a combined therapy with amiodarone and beta-blockers) and in patients who had cardiac arrest.

All patients were followed at four-week intervals. The mean duration of follow-up was 23 ± 14 months. At each visit, they underwent physical examination, basal ECG, two-dimensional echocardiogram, and Holter monitoring.

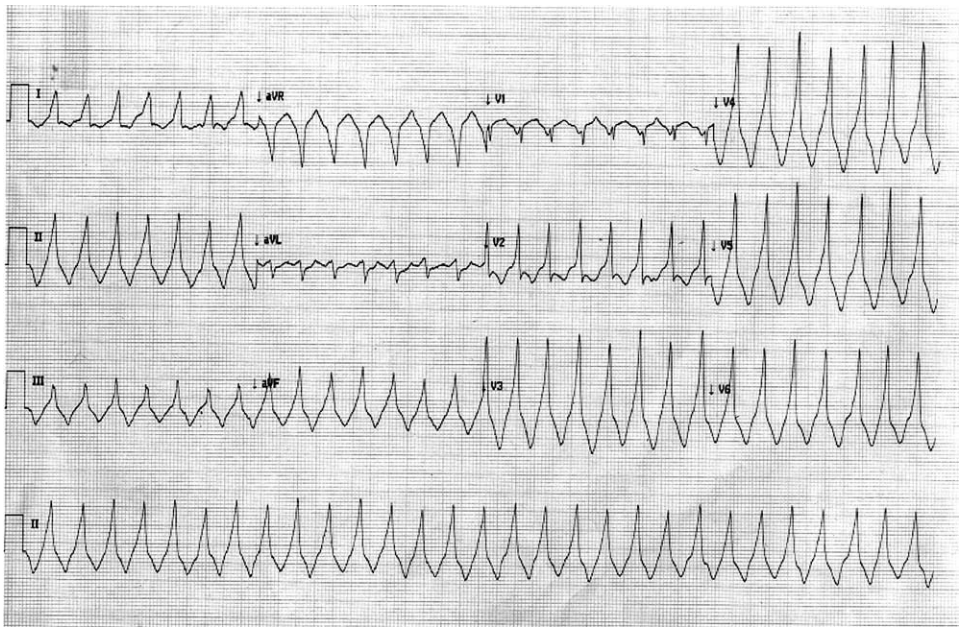

Figure 1. 12-lead electrocardiogram from a 27-year-old man with palpitations, showing a sustained ventricular tachycardia with left bundle branch block morphology.

The progression of the disease was evaluated on the basis of a worsening in RV structural and functional abnormalities with an eventual involvement of the LV by the pathologic process and on the basis of the increased electrical instability despite the medical treatment.

Statistical analysis. All values are expressed as mean ± SD. A value of $p < 0.05$ was considered significant. Significance between two values was determined by Student *t* test for unpaired data and by chi- square test. Comparison between groups was performed by the analysis of variance, with the Bonferroni *t* test correction, and all the p values were Bonferroni-corrected. A total of three comparisons were included in the correction.

RESULTS

Clinical studies. All 30 patients were admitted because of the presence of ventricular arrhythmias with left bundle branch block morphology (Figs. 1 and 2), in absence of family history of ARVD. In addition, ECG and echocardiographic screening of first-degree family members was negative.

Two (6.7%) patients were resuscitated from a cardiac arrest due to ventricular fibrillation, 10 patients (33%) presented episodes of sVT, 10 patients (33%) nsVT, and 8 (27%) frequent ventricular ectopic beats (>1,000/24 h on Holter monitoring). None had a family history of premature

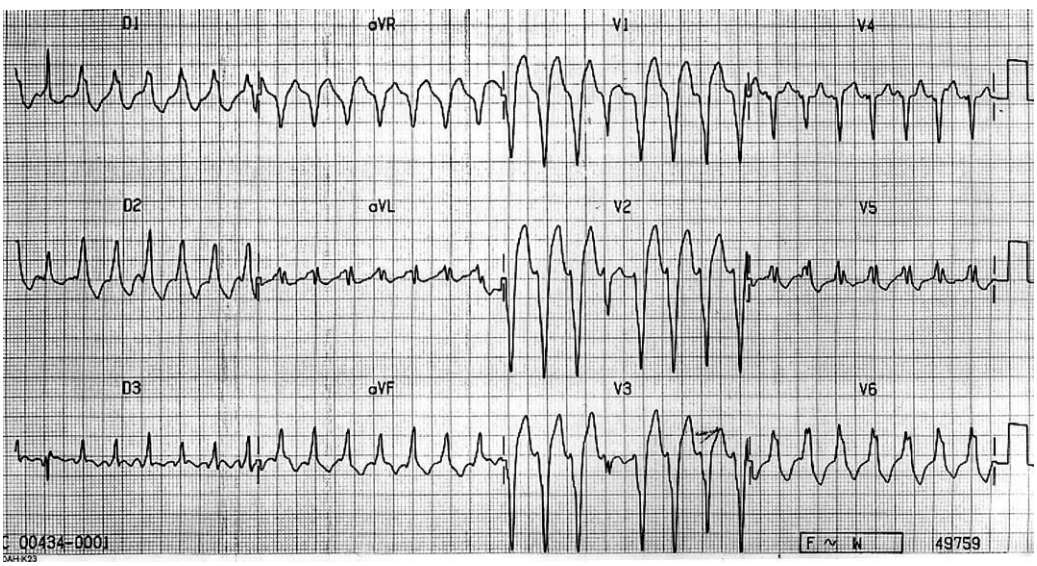

Figure 2. 12-lead electrocardiogram from a 29-year-old woman presenting with syncope, showing a sustained ventricular tachycardia with left bundle branch block pattern.

JACC Vol. 43, No. 12, 2004
June 16, 2004:2305–13

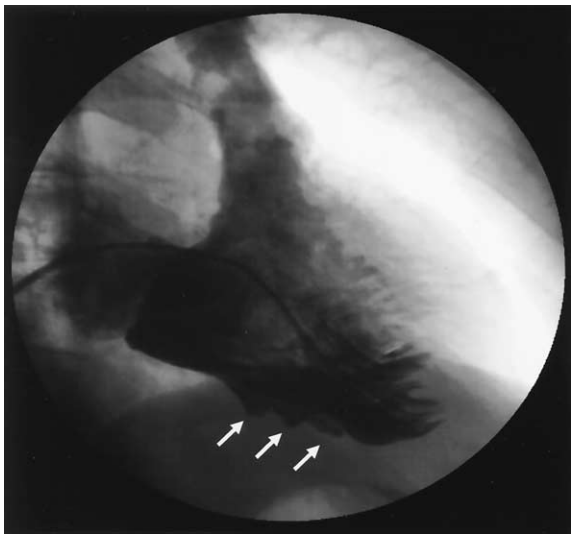

Figure 3. Right ventricular angiography (20° right anterior oblique projection) from patient of Figure 1, showing multiple small aneurysms of the inferior wall.

sudden death or cardiomyopathy. Among the 30 patients, 21 (70%) showed depolarization/conduction abnormalities, including the presence of epsilon waves (2 patients) or localized prolongation of the QRS complex in right precordial leads (QRS ≥110 ms) (13 patients) and/or the presence of late potentials at signal-averaged ECG (11 patients). Inverted T waves on right precordial leads (V_1 to V_3) were present in eight (27%) patients.

All 30 patients showed global and/or regional dysfunction and structural alterations of the RV detected by echocardiography, angiography, and MRI (Figs. 3 and 4). In particular, global RV dilation and dysfunction were detected in 23 patients (77%), being of severe degree in 6 patients (echocardiographic end-diastolic diameter = 36 ± 5 mm; ejection fraction = 31 ± 4%) and mild in the remaining 17

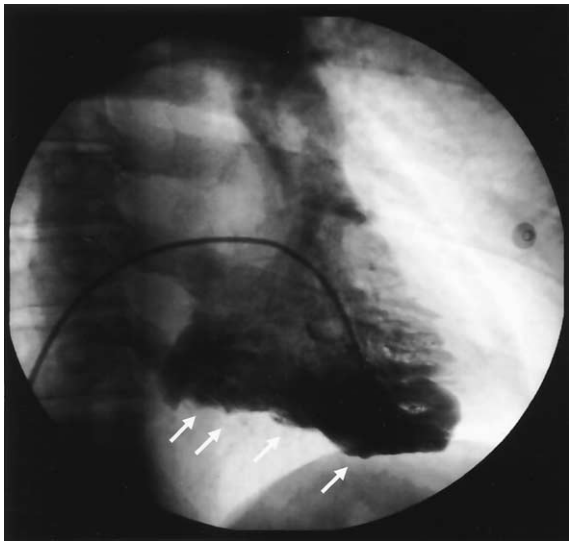

Figure 4. Right ventricular angiography (30° right anterior oblique view) from patient of Figure 2, showing small localized aneurysms of the inferior and posterior wall.

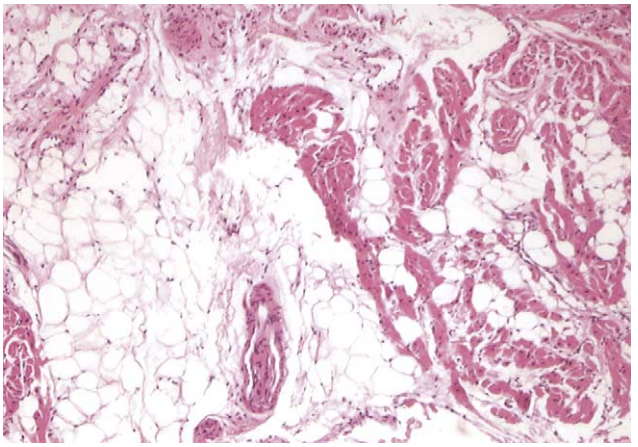

Figure 5. Right ventricular endomyocardial biopsy from patient of Figures 1 and 3, showing a severe fibrofatty infiltration of the myocardium, suggesting an arrhythmogenic right ventricular dysplasia (hematoxylin eosin 100×).

patients (end-diastolic diameter = 29 ± 6; ejection fraction = 45 ± 7%). Segmental RV dilation with localized areas of hypokinesia were present in seven patients (23%), of severe degree in two, and mild in five. Left ventricular dimensions and global function were normal in all cases. Localized wall motion abnormalities of the LV were present in three cases (10%).

Single or multiple localized aneurysms were detected in 19 patients (63%) by angiography and MRI and were located in the inferior and inferobasal RV wall, at the apex and in the anterior RV wall.

At MRI, focal or diffuse intramyocardial areas of high-signal intensity in T1-weighted images, considered suggestive of fatty tissue infiltration, were detected in 19 patients (63%). In particular, MRI showed hyperintense signals in 67% of ARVD and in 62% of the myocarditis group. The diffuse or focal hyperintense signal areas were localized in the apex and in the subtricuspid walls of the RV, and/or in the pulmonary infundibulum (triangle of dysplasia).

Each patient received a diagnosis of ARVD on the basis of two major criteria (12 patients, 40%) and of one major plus at least two minor criteria (18 patients, 60%). Because of the lack of specificity of the interpretation of MRI studies in patients with suspected ARVD, as recently shown by Bluemke et al. (12), the data from the MRI studies were not used for any of the diagnostic criteria.

Histologic findings. The diagnosis of ARVD was confirmed by histologic findings in nine patients (30%). Conversely, focal inflammatory infiltrates with necrosis of the adjacent myocytes, meeting the Dallas criteria for myocarditis, associated with various amounts of interstitial and replacement fibrosis, were present in all specimens taken from the RV in the other 21 (70%) (Figs. 5 and 6). Immunohistochemical staining confirmed the presence of myocarditis. Morphometric analysis (Fig. 7) showed a reduction in percent area of myocytes in ARVD patients compared with myocarditis (44 ± 9.2% and 68.2

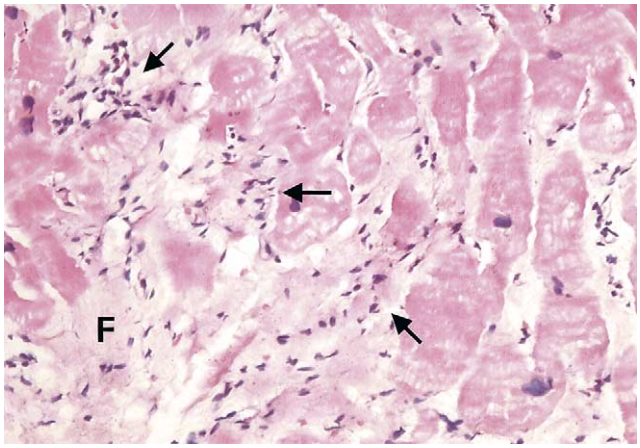

Figure 6. Endomyocardial biopsy from the right ventricle from patients of Figures 2 and 4, showing an active lymphocytic myocarditis **(arrows)** (HE 250×) with areas of interstitial and replacement fibrosis (F).

± 9.8%, respectively, $p < 0.001$) with an increase in adipose tissue (24 ± 7.8% vs. 0.3 ± 0.6%, $p < 0.001$) and comparable values of fibrosis (26 ± 11.1% vs. 20 ± 7.8%, p = NS). The morphometric analysis was a mean of the evaluation of all the specimens drawn from different sites of the RV. There was a difference in the percentage of fat among the different specimens, having the biopsies from the areas with more prominent structural abnormalities a more evident fatty replacement of the myocardium. However, the range of values was from 8% to 45%, showing also in the specimens drawn from the interventricular septum a percentage of adipose tissue diagnostic for ARVD (Table 1). Control values for these parameters were 88.9 ± 3.5% for myocytes ($p < 0.001$ vs. ARVD, $p < 0.001$ vs. myocarditis), 4.9 ± 2.5% for fibrous tissue ($p < 0.001$ vs. ARVD, $p < 0.001$ vs. myocarditis), and 0.33 ± 0.8 % for adipose tissue ($p < 0.001$ vs. ARVD, p = NS

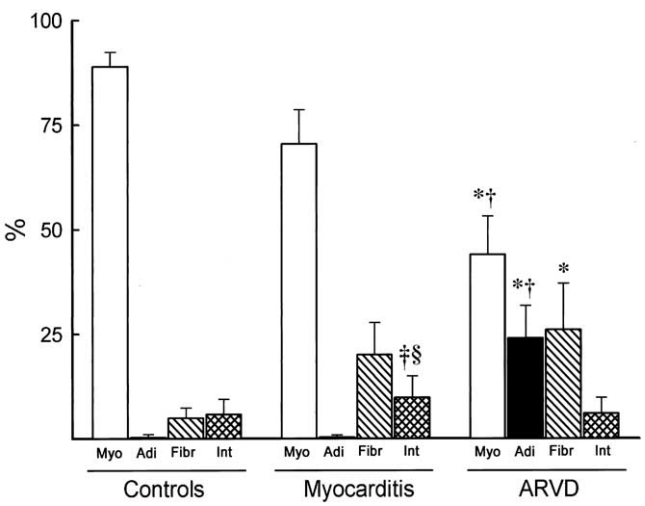

Figure 7. Percentage of myocytes (Myo), adipose tissue (Adi), fibrosis (Fibr), and interstitium (Int) (other interstitial structures not including adipose and fibrous tissue) in the myocardium of controls, myocarditis, and arrhythmogenic right ventricular dysplasia (ARVD). Results are mean ± SD. *$p < 0.001$ ARVD vs. controls; †$p < 0.001$ ARVD vs. myocarditis; ‡$p < 0.05$ myocarditis vs. controls; §$p < 0.05$ myocarditis vs. ARVD.

vs. myocarditis). Patchy inflammatory infiltrates were present in the RV of four patients with ARVD (44%). The total number of CD45-positive cells and CD3-positive lymphocytes revealed abnormal values in all the RV biopsies from patients with myocarditis (CD45 = 8.2 ± 2.7 per HPF, CD3 = 3.8 ± 1.06 per HPF) and in the RV of the four patients with ARVD (CD45 = 5.6 ± 1.3; 2.15 ± 0.45 per HPF). Control values for these parameters were: CD45 = 1.12 ± 0.5 per HPF, CD3 = 0.5 ± 0.3 per HPF. The quantification of the inflammatory infiltrates showed a difference between specimens drawn from areas with normal contractility and areas with wall motion abnormalities, both in ARVD and in myocarditis patients (Table 1).

The LV samples of all patients with ARVD were normal. Conversely, in 10 patients (48%) with RV myocarditis, an LV focal inflammation was detected. Among these 10 patients, 3 had localized LV wall motion abnormalities.

No complications related to EMB occurred in our patients, and no mesothelial cells, suggesting myocardial perforation, were observed in any of the specimens.

Comparing the ECG-arrhythmic and morphofunctional criteria of diagnosis in the two groups of patients, no statistically significant difference was detected for any of these parameters, as shown in Table 2.

Molecular biology studies. In all patients, the presence of sufficient target nucleic acid was confirmed by amplification of beta-globin for deoxyribonucleic acid and 3GPDH for ribonucleic acid. No viral genomes were detected in the myocardium of patients with ARVD. Four of the 21 patients with myocarditis (19%) were positive for myocardial viruses, including enterovirus (2 patients) and adenovirus (2 patients). None of the five controls was positive for any virus. Sequencing analysis of the PCR amplimers showed a high homology with Coxsackie virus B3 and adenovirus 2 and 5.

Treatment and follow-up. Treatment and follow-up of 30 patients with clinical profile of ARVD are reported in Table 3.

Patients with frequent and complex PVB and with nsVT were treated with sotalol 240 mg (15 patients) or metoprolol 200 mg (3 patients). Patients with sVT were treated with sotalol 240 mg (seven patients) and amiodarone 400 mg (three patients). Two patients resuscitated from cardiac arrest at the time of admission (one with ARVD and one with myocarditis) received an ICD.

At a mean follow-up of 23 ± 14 months in patients with myocarditis, arrhythmias were controlled by antiarrhythmic drugs, and no detectable disease progression was observed. In particular, no localized or diffuse increase in the RV dimension and no segmental or global reduction of RV function from the baseline echocardiographic measurement was detected. Conversely, life-threatening arrhythmias not controlled by antiarrhythmic drug therapy, consisting of a combination of amiodarone and metoprolol, required ICD implantation in five patients with ARVD. In these patients, the arrhythmias

Table 1. Morphometric Data and Quantification of the Inflammatory Infiltrates of Patients With ARVD and Myocarditis in Normokinetic and Ipo-Dyskinetic Right Ventricular Biopsy Sites

	Myocytes % Area N-A	Adipose Tissue % Area N-A	Fibrous Tissue % Area N-A	Interstitium % Area N-A	Inflammatory Inf CD3+ Cells/HPF N-A
ARVD patients					
1	44%-33%	23%-31%	28%-34%	5%-2%	0-0
2	52%-29%	26%-45%	12%-15%	10%-11%	0-3.2
3	52%-35%	18%-25%	22%-35%	8%-5%	0-0
4	55%-33%	19%-33%	18%-32%	8%-2%	0-2
5	60%-41%	8%-22%	16%-33%	16%-4%	0-2.5
6	46%-30%	19%-39%	21%-31%	14%-1%	0-0
7	58%-34%	15%-22%	23%-41%	4%-3%	0-0
8	59%-35%	21%-32%	12%-32%	8%-1%	0-2
9	63%-33%	10%-25%	20%-40%	7%-2%	0-0
Myocarditis patients					
1	80%-78%	0%-0%	10%-18%	10%-4%	3-6.2
2	69%-51%	0.5%-1%	16%-30%	14.5%-18%	3.5-5.5
3	82%-55%	0.5%-0%	10%-29%	7.5%-16%	2-4.5
4	70%-57%	0%-0%	20%-28%	10%-15%	2.5-5
5	80%-50%	1.5%-0%	10%-34%	8.5%-16%	2-5.3
6	71%-59%	0%-0%	12%-22%	17%-19%	3.6-5.1
7	75%-59%	2%-0.5%	15%-30%	8%-10.5%	3-6.2
8	73%-60%	0%-0%	13%-24%	14%-16%	3.2-5.2
9	74%-60%	0%-0%	14%-23%	12%-17%	3.5-7
10	74%-60%	0%-0%	15%-24%	11%-16%	2.6-6
11	75%-60%	0%-1.5%	15%-25%	10%-13.5%	2.1-4.1
12	76%-63%	0%-1%	16%-25%	8%-11%	2.6-4.8
13	76%-63%	0%-0%	16%-28%	8%-9%	2-3.5
14	78%-59%	0%-0%	17%-29%	5%-12%	2-5
15	79%-64%	0%-0.5%	18%-30%	3%-5.5%	2.2-4.5
16	83%-65%	0%-0%	11%-28%	6%-7%	2.5-6
17	81%-65%	0%-0%	10%-11%	9%-14%	2-3.5
18	80%-65%	0%-2%	12%-31%	8%-2%	3-5
19	77%-66%	0%-0%	19%-21%	4%-13%	3.3-8
20	70%-63%	0%-0%	20%-30%	10%-7%	2-6
21	94%-67%	0%-0%	4%-20%	2%-13%	2.5-6.5

A = abnormal wall motion (ipo/dyskinetic) areas; ARVD = arrhythmogenic right ventricular dysplasia; HPF = high-power field (400-fold magnification); Inf = infiltrates; N = normokinetic areas; pts = patients.

consisted of frequent episodes of sVT symptomatic for palpitation in three cases and for syncope in two. In three of these five patients, a morphologic progression of the disease was detected, consisting of an increase in RV global dimension in one patient (end-diastolic diameter from 29 to 33 mm) with reduction of RV function (ejection fraction from 40% to 32%) and in the appearance of a previously absent localized area of RV hypokinesia in the remaining two patients, one of them associated with LV apical hypokinesia. In the remaining cases of ARVD, no disease progression was detected.

DISCUSSION

Arrhythmias originating from the RV myocardium can be caused by several cardiac disorders (13). In order to distinguish ARVD from other cardiac pathologies, the diagnostic criteria established in 1994 included the demonstration of abnormal fibrofatty replacement of the RV myocardium on EMB samples (3). However, the role of EMB is still questioned (14,15) because: 1) the low sensitivity of septal biopsies, as the septal involvement is uncommon; 2) the risk of perforation of the RV free wall during the procedure; and 3) the segmental distribution of the RV alteration particularly at the early stage of the disease.

In our study we tried to overcome sampling limitation performing multiple biopsies even on RV free wall and approaching particularly those areas with wall motion abnormalities.

In addition, EMBs were 2 to 3 mm in depth, representing RV thickness to a large extent and making it unlikely that ARVD lesions would be missed.

In our study, histology was diagnostic for ARVD in nine patients (30%), being the typical findings more evident in the samples from the regions close to the structural and functional RV anomalies.

Conversely, an RV myocarditis was detected in 70% of cases in the absence of fatty replacement of the RV myocardium consisting of ARVD, even in the biopsies drawn from the areas with documented RV abnormalities. This group of patients was affected by a prevalent right-

Table 2. Electrocardiographic-Arrhythmic and Morphofunctional Parameters of Patients With ARVD Compared With Patients With Myocarditis

	Myocarditis (n = 21)	ARVD (n = 9)	*p
Mean age (yrs)	26 ± 10.8	29 ± 7	NS
Gender (M, F)	9 (43%), 12 (57%)	5 (55%), 4 (44%)	NS
Ventricular fibrillation	1 (5%)	1 (11%)	NS
Sustained ventricular tachycardia	7 (33%)	3 (33%)	NS
Nonsustained ventricular tachycardia	7 (33%)	3 (33%)	NS
Premature ventricular beats	6 (29%)	2 (22%)	NS
Depolarization/conduction abnormalities	11 (52%)	3 (33%)	NS
Repolarization abnormalities	5 (24%)	3 (33%)	NS
Right ventricular dilation			
Global			
Severe/mild	4 (19%)/12 (57%)	2 (22%)/5 (55%)	NS
Segmental			
Severe/mild	1 (5%)/4 (21%)	1 (11%)/1 (11%)	NS
Right ventricular hypokinesia			
Global			
Severe/mild	4 (19%)/12 (57%)	2 (22%)/5 (6%)	NS
Segmental			
Severe/mild	1 (5%)/4 (19%)	1 (11%)/1 (11%)	NS
Right ventricular aneurysms	13 (62%)	6 (67%)	NS

*$p < 0.05$ was considered significant.
ARVD = arrhythmogenic right ventricular dysplasia.

sided myocarditis simulating the clinico-instrumental characteristics of an ARVD.

In a study by Witcher et al. (16), findings supporting the diagnosis of RV dysplasia, which were defined as an abnormal fibrolipomatous or adipose tissue infiltration exceeding an area of 25% in one or more biopsy specimens, were present in 31 of 47 patients (66%). Nonspecific findings were found in 3 patients (6%), and EMB was normal in the remaining 13 patients (28%). There was no evidence of an acute myocarditis or storage disease in any patient. These results are at variance with the findings detected in the present study. No major complications, as cardiac perforation, occurred in our experience despite an extensive biventricular study.

Thus, in sporadic cases of ARVD, the histologic study seems the most appropriate, and even safe, approach to reach a correct diagnosis.

Accepted standard clinical and instrumental criteria for ARVD. Echocardiography, angiography, and MRI are the most commonly used techniques for the diagnosis of ARVD. In particular, RV angiography is considered a diagnostic reference standard. Localized areas of akinesia or dyskinesia in the apex, inferior and anterior wall, and global or segmental RV dilation and systolic dysfunction (17) are considered diagnostic of ARVD. However, in our series, such angiographic abnormalities were detected with a similar prevalence in both ARVD and myocarditis. In particular, RV aneurysms in the so-called "triangle of dysplasia" (18), considered to be pathognomonic of ARVD, were present also in 62% of patients with myocarditis. This finding is consistent with the reported occurrence of inflammatory ventricular aneurysms, localized in the RV or in the LV, both in experimental models of myocarditis and in humans (5–19).

More recently, cardiac MRI has been proposed as the most accurate noninvasive diagnostic technique for ARVD (20). In our series, MRI did not differentiate patients with ARVD from patients with myocarditis. In particular, the detection of the hyperintense signal in T1-weighted images was not diagnostic of ARVD, possibly because the hyper-

Table 3. Arrhythmic Profile, Histology, Treatment, and Follow-Up of 30 Patients With Clinical Profile of ARVD

Arrhythmias	Number of Patients	Histology	Treatment at Discharge	Follow-Up
VF	2	ARVD = 1 (11%); M = 1 (5%)	ICD = 1 ARVD (11%), 1 M (5%)	U = 1 ARVD (11%), 1 M (5%)
sVT	10	ARVD = 3 (33%); M = 7 (78%)	Sotalol = 2 ARVD (22%), 5 M (24%) Amiodarone = 1 ARVD (11%), 2 M (9%)	U = 7 M (33%) ICD = 3 ARVD (33%)
nsVT	10	ARVD = 3 (33%); M = 7 (78%)	Sotalol = 2 ARVD (22%), 6 M (29%) Metoprolol = 1 ARVD (11%), 1 M (5%)	U = 1 ARVD (sotalol) (11%), 7 M (33%) ICD = 2 ARVD (22%)
PVB	8	ARVD = 2 (22%); M = 6 (29%)	Sotalol = 2 ARVD (22%), 5 M (24%) Metoprolol = 1 M (5%)	U = 2 ARVD (22%), 6 M (29%)

ARVD = arrhythmogenic right ventricular dysplasia; ICD = implantable cardioverter device; M = myocarditis; ns = not sustained; PVB = premature ventricular beats; s = sustained; U = unmodified; VF = ventricular fibrillation; VT = ventricular tachycardia.

intense signals are not specifically related to adipose tissue but may derive from other structural lesions, including myocardial edema and/or inflammation (21,22). Another explanation (11) can be an erroneous interpretation of the hyperintense signal because of the huge interobserver variability in the evaluation of the MRI findings. Therefore, cardiac MRI can be misleading if used as an elective tool for the morphologic analysis of myocardial tissue in patients with RV arrhythmias.

ARVD and RV myocarditis. Patchy inflammatory infiltrates were detected in four of nine patients with ARVD (44%), raising the possibility of an infectious/inflammatory etiology of the disease. According to this theory, ARVD might result of a primary myocarditis, being the disappearance of the RV myocardium as the consequence of an inflammatory necrotic injury followed by a fibrofatty repair (23). This hypothesis, based on the frequent detection of inflammatory infiltrates in patients with ARVD is, however, not universally accepted, because the inflammation could be a secondary event not implicated in the pathogenesis of the disease. In other terms, an already diseased myocardium can have an increased susceptibility to viral infection (24) with resulting myocardial inflammation that can eventually play a role in the clinical manifestations of the disease, increasing the risk of arrhythmias (25,26).

Anyway, this was not the case in 70% of our patients in which myocarditis, incorporating various amounts of interstitial and replacement fibrosis thus suggesting a reparative phase, was detected in the absence of fatty replacement. Moreover, inflammatory infiltrates were not found in LV EMB in any of the patients with ARVD, but in 48% of patients with myocarditis. Viruses, the most commonly established causal agents of myocarditis, were not found in any of the patients with ARVD, but were detected in 19% of patients with histologic diagnosis of myocarditis, this finding being at variance with Bowles et al. (24) who detected virus sequences in 58% of patients with sporadic ARVD. The relatively low percentage of viral genome detection may be related to the long-time interval between viral infection and time to biopsy, being the presence of replacement fibrosis at histology, suggestive of a chronic phase of the myocardial inflammation.

Finally, during follow-up, none of the patients with myocarditis showed a detectable morphologic and arrhythmogenic progression of the disease.

In conclusion, we believe that our patients were affected by two different diseases: 30% by an ARVD and 70% by a predominantly right-sided myocarditis simulating the clinical and instrumental characteristics of an ARVD, as already described in several case reports (27–29).

It is known that myocarditis in its clinical spectrum may present with even severe ventricular arrhythmias. The myocardial inflammation can involve selectively the RV (30) giving rise to RV electric instability and structural or functional abnormalities involving selectively the right side of the heart. The significance of inflammatory infiltrates in ARVD remains a controversial issue that still waits for a conclusive explanation.

Clinical implications. Over 50% of cases of ARVD are sporadic (31). In the absence of a family history, patients with clinical and instrumental diagnosis of ARVD may well be affected by a myocarditis involving predominantly the RV. These two conditions have often different prognosis and treatment. The former is a progressive entity where major clinical intervention, as ICD implantation, or heart transplantation may be required, while the latter is often a self-limited process responding usually to a conservative approach.

Reprint requests and correspondence: Dr. Andrea Frustaci, Cardiology Department, Catholic University, Largo A. Gemelli 8, 00168 Rome, Italy. E-mail: biocard@rm.unicatt.it.

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