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# Anatomical features and clinical correlations in caucasian patients with definite arrhythmogenic right ventricular dysplasia/cardiomyopathy

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***Aim.*** **Arrhythmogenic right ventrticular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by fibrofatty replacement and a high risk of ventricular arrhythmias (VA) and sudden cardiac death (SCD). The aim of the present investigation is to examine the pathological profile and the clinical correlations in a group of ARVD/C patients.**

***Methods.*** **We conducted a multicenter study evaluating 47 patients (31 men; mean age 37±14 years) with definite ARVD/C. Diagnosis was established according to the actual clinicomorphologic criteria at autopsy or clinically. We divided the study population in 2 different groups. First group included 28 alive patients and the second 19 patients dead suddenly.**

***Results.*** **Age at presentation was different in the two groups (P=0.0015). We observed an important association regarding the risk of sudden death and the history of physical exercise (P=0.0017). Moreover patients with negative outcome (i.e., SCD, cardiac transplantation, congestive heart failure) had a significantly association with biventricular form of ARVD/C (P=0.0034) and age presentation (P=0.003). Left ventricular (LV) involvement was frequently observed in the two groups (17% and 32% respectively). Postmortem examination revealed frequent inflammatory infiltrates (26%) indicating active myocarditis, which probably justify the fatal arrhythmic events occurred in these patients.**

***Conclusion.*** **Frequent LV involvement justifies the recent adoption of the broad term Arrhythmogenic Cardiomyopathy. Early age presentation, sport activity and the biventricular form of ARVD/C represent important predictors of adverse outcome that can be useful to early identify patients at high risk.**

**Key words:** Cardiomyopathies - Death, sudden - Young adult - Exercise.

Arrhythmogenic right ventrticular dysplasia/cardiomyopathy (ARVD/C), is a rare inherited cardiomyopathy, with an estimated prevalence in the general population of 1 per 5000.[1] ARVD/C is typically transmitted as an autosomal dominant trait with variable penetrance and the pathologic hallmark is a progressive right ven-

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tricular (RV) myocyte loss with fibrofatty replacement, especially regarding the apex, inflow and outflow tracts (so-called "triangle of dysplasia").[2, 3] Postmortem examination of patients with ARVD/C often shows RV myocardial atrophy with wall thinning, aneurysms, and global dilation of the RV. However left ventricular is so frequently involved, justifying the adoption of the broad term "arrhythmogenic cardiomyopathy".[4] Many studies showed that genetic mutation alterating desmosomal and non desmosomal proteins underlie the histopathological changes leading to the progressive myocardiocite loss.[5, 6] Histological alterations interfere with the normal conduction of electrical impulses, thus leading to electrical instability and frequently to ventricular arrhythmias (VA), which worsen patients' prognosis by increasing their risk of a sudden cardiac death (SCD) especially in young people and athletes. Sports activity has been shown to increase the risk of sudden death in people with ARVC by five-fold, since acute volume overload and stretching of the right ventricle during effort as well as sympathetic stimulation are major triggers of life-threatening arrhythmias. Diagnosis is established according to the Task Force diagnostic criteria revised on 2010.[7] The aim of this multicenter study is to examine the clinicopathologic profile of ARVD/C in a group of affected patients. For this reason we analyzed two group of patients with different clinical onset presentation. In the first group diagnosis was established *in vivo*, in the second at autopsy in patients died suddenly for lethal VA.

## Materials and methods

### *Study population*

The study population consists of 2 groups. First group included 28 patients (18 male; mean age 42±14 years), and the second group 19 patients (13 male; mean age 29±10 years). Patients were enrolled at 6 collaborative medical centers. Upon their clinical onset presentation they were divided in two different groups. In both cases diagnosis was established according to the specific clinocopathologic protocols developed by the revised Task Force criteria.[7] Definite diagnosis of ARVD/C was based on the presence of either 2 major or 1 major and 2 minor. Diagnosis was considered borderline when 1 major and 1 minor or 3 minor criteria from different categories were fulfilled. To enhance the diagnostic specificity no patient with only minor criteria and borderline diagnosis entered the study. Patients whose diagnosis was based on the original 1994 diagnostic criteria,[8] were reviewed upon the latest to confirm or exclude the diagnosis.

### *First group*

All medical records of each patients were carefully reviewed for information regarding demographics, detailed family history, presenting symptoms, electrocardiographic abnormalities on a 12-lead electrocardiogram, 24-h Holter monitoring, clinical arrhythmic events (syncope, ventricular fibrillation [VF], ventricular tachycardia). Echocardiographic and magnetic resonance (MR) imaging were obtained for a correct evaluation of the structural abnormalities and the extent of right ventricular dysfunction. Right ventricular angiography and/or endomyocardial biopsy were performed under discretion of the managing cardiologists, such us programmed ventricular stimulation. Patients' management therapy was established according to the clinical features and risk stratification of each patient considering drug therapy, ICD implantation, catheter ablation and cardiac transplantation. Follow-up data were available for all 28 study patient. Patients were followed up at each collaborative medical center at biannual and yearly intervals. Data included invasive and non invasive investigation, clinical arrhythmic events, quality of life and device interrogation.

All patients provided written informed consent before joining the study. The authors of this manuscript have certified that all experiments were performed in strict

compliance with the 2008 Helsinki Declaration amendment on ethics requirements.

### Second group

Analysis of macroscopic and histopathologic abnormalities of ARVD/C derived from a systematic study performed by the "Department of Legal Medicine" of the "P. Giaccone Hospital", on entirely hearts of patients died suddenly at postmortem examination. Sudden death was defined as an unexpected natural phenomenon in which loss of all vital functions occurred instantaneously or within 1 hour of the onset of symptoms. Macroscopic examination included measurement of heart weight and wall thickness. The following regions were systematically examined: apex, inflow and outflow tracts of RV, posterolateral and anterolateral walls of both ventricles and interventricular septum. The morphologic changes that we addressed were wall thinning, cavity enlargement or aneurysm, myocardial atrophy and fatty or fibrofatty replacement. RV involvement was considered widespread or regional upon the pathologic extension of the disease. Histologic examination was performed from each region of the right and left ventricles and the septum. All myocardial section were formalin-fixed and paraffin-embedded and stained with hematoxylin-eosin or with Mallory-Azan stain. The following morphologic lesions were assessed in the histologic specimens: myocardial atrophy, fatty or fibrofatty replacement, myocite degeneration (necrosis, apoptosis, myocytolysis) and interstitial cell infiltrates. No ECG or cardiac imaging data were available for this patients.

### Statistical analysis

Results are expressed as mean±SD. Comparisons between groups of patients were made using Student t-test or one-way ANOVA. Categorial variables are reported as frequency (percentage) and compared between groups by the chi-square or Fish exact test. A P value $<0.05$ was considered significant.

## Results

### Demographic findings

The first group included 28 patients (18 male; 64.3%) with an age at time of diagnosis ranged from 17 to 68 years (mean age 42±14 years). The second group included 19 patients (13 male; 68.4%) and the age at time of death ranged from 16 to 43 years (mean age 29±10 years). Baseline clinical characteristics are summarized in Table I.

### Imaging findings of the living group

All 28 patients of the living group underwent ultrasound (US) examination for a correct evaluation of the structural abnormalities and the extent of right ventricular dysfunction. Wall motion abnormalities of the RV (akinesis/dyskinesis) was observed in 26 patients (93%) especially in the apex, inflow and outflow tracts (RVOT). Twenty-two patients (79%) showed an hypertrophic RV trabeculation with diastolic bulging of the free wall in 8 patients (29%). RVOT values were frequently increased (35.6±6.6 mm in parasternal long-axis view, PLAX).

Table I.—*Baseline clinical characteristics of the study population.*

| Clinical characteristics | Living patients | Sudden death | P value |
|---|---|---|---|
| Age at presentation (mean±SD) | 42±14 | 29±10 | 0.0015 |
| Male (N.; %) | 18 (64.2%) | 13 (68.4%) | 0.98 |
| Symptomatic at presentation/before death (N.; %) | 27 (97%) | 1 (5%) | 0.00001 |
| Biventricular involvement (N.;%) | 5 (17%) | 6 (32%) | 0.45 |
| History of sport activity (N.; %) | 5 (17%) | 14 (74%) | 0.0004 |
| Family History of sudden death (N.; %) | 8 (28%) | 0 (0%) | 0.03 |
| Family History of ARVD/C (N.;%) | 3 (11%) | 0 (0%) | 0.38 |

MR was performed in 25 patients (89%), and in all patients there was at least 1 or more abnormal MR sign. The most frequent abnormalities were focal right ventricular diskinesia (21 patients; 84%), fatty infiltration (23 patients; 92%), right ventricular aneurysm (10 patients; 40%). Abnormal enhancement in the RV wall on the delayed enhancement images was observed in 16 patients (84%). In 5 patients (17%) was found a biventricular involvement with focal left ventricular diskinesia and fatty infiltration.

### *Clinical outcome of the living group*

In the first group 8 patients (28%) had a family history of sudden death and 3 patients (11%) of ARVD/C. In almost all cases we observed a symptomatic presentation not correlated with precipitating factors. Only 2 patients (7%) referred physical exercise before symptoms onset and 3 patients (10%) were competitive athletes. Finally only 1 patient (3%) was asymptomatic. Symptoms more frequently referred were palpitation and syncope (13 patients in both cases; 46%), presyncope (8 patients; 28%), cardiac arrest (5 patients; 18%), dizziness (4 patients; 14%), chest pain (3 patients; 10%), dyspnea (2 patients; 7%), signs and symptoms of RV failure (1 patients; 3%). We studied our patients over a mean follow-up of 6.0±4.4 years. To this date no mortality was reported. At the time of the diagnosis more than half patients (15 patients, 54%) received an ICD implantation based to the estimated risk of SCD according with the last guidelines for management of patients with ventricular arrhythmias.[9] ICD implantation was associated with antiarrhythmic agents in 13 patients (87%). Radiofrequency catheter ablation for the treatment of ventricular arrhythmias was performed in 6 patients (21%). During the follow-up, 8 patients (61%) received an ICD implantation because of the relapse of arrhythmic events although they were using antiarrhythmic drugs or underwent catheter ablation for VT. Of the 23 patients who received an ICD, 20 (86%) had received appropriate ICD therapy (Figure 1). An appropriate ICD shock intervention for ventricular fibrillation (VF)/ventricular flutter (VFL) was seen in 12 patients (52%). Two patients (7%) underwent cardiac transplantation as a final therapeutic option due to refractory congestive heart failure and 1 patients (3%) was placed on a waiting list.

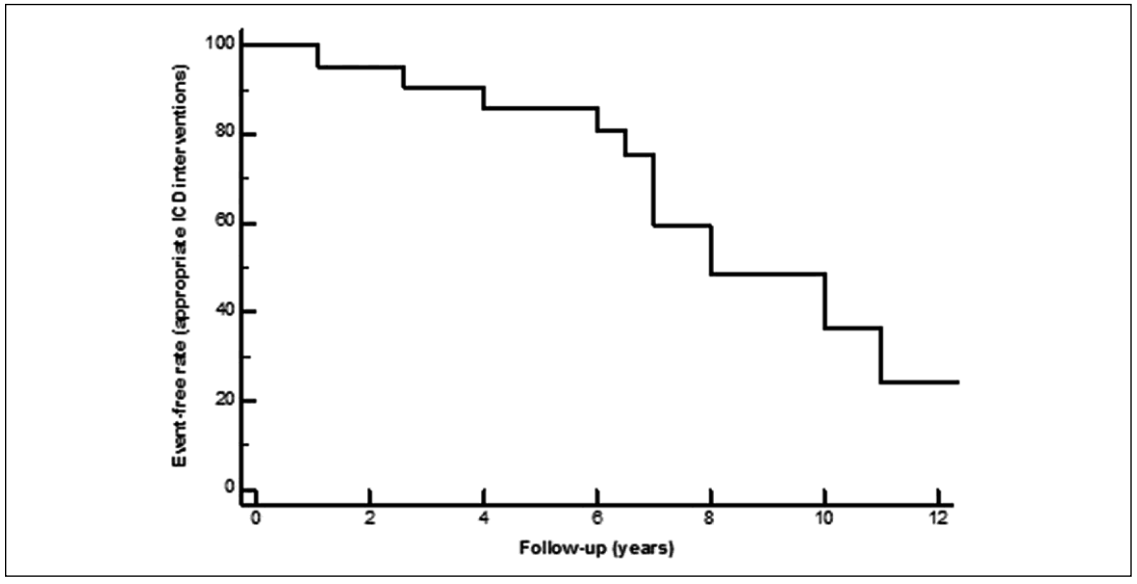


Figure 1.—Kaplan-Meier analysis of appropriate ICD interventions.

### *Clinical outcome of the sudden death group*

In the second group no patients had a family history of sudden death or ARVD/C. Sudden cardiac death represented the first clinical presentation of ARVD/C in 18 patients (95%), only 1 patient (5%) had an history of premature ventricular contractions (PVC). In whole patients death occurred immediately (within 1h from symptoms onset): in 14 patients (74%) occurred during physical exercise and in 5 patients (26%) occurred at rest. Eleven patients (58%) were competitive athletes.

### *Results correlations*

Comparing the two groups results an important difference in terms of age presentation. Indeed there is a statistically significant difference between the mean ages at presentation (42±14 years *vs.* 29±10 years; P=0.0015). We observed moreover how the event of death occurred as frequently as early is the onset of the disease (Figure 2).

No significant differences existed between the risk of sudden death and the male sex. We observed moreover an important difference regarding the risk of sudden death and the history of physical exercise (78.5% vs. 24%; P=0.001), suggesting the improved risk of SCD deriving from sport activity. We finally analyzed patients with negative outcome (SCD, cardiac transplantation, congestive heart failure). We found a significantly association with biventricular form of ARVD/C and age presentation. The risk of adverse outcome is more frequent in patients with a biventricular involvement of the disease (46% vs. 4%; P=0.0034) and in patients with an early age presentation (P=0.003; Figure 3).

### *Pathological findings*

Gross morphologic features

Analysis of pathologic abnormalities of ARVD/C was performed on 19 hearts at necropsy study (Table II).

Hearts showed a mean weight of 370±66.5 g (range from 270 to 470 g). On external examination right side appeared yellowish with grayish nuances. In 5 cases (26%) were identified aneurismal dilatation of RV wall at one or more of the following locations: RV outlet in 3 cases (16%), RV inlet in 1 case (5%) and apex in 1 case (5%).

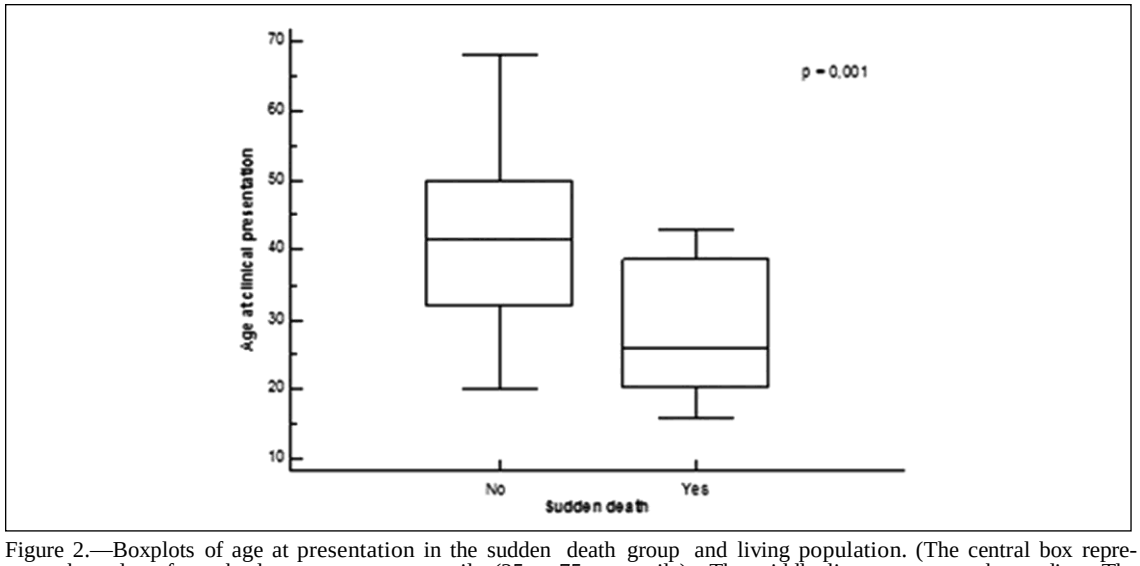


Figure 2.—Boxplots of age at presentation in the sudden death group and living population. (The central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The vertical line extends from the minimum to the maximum value).

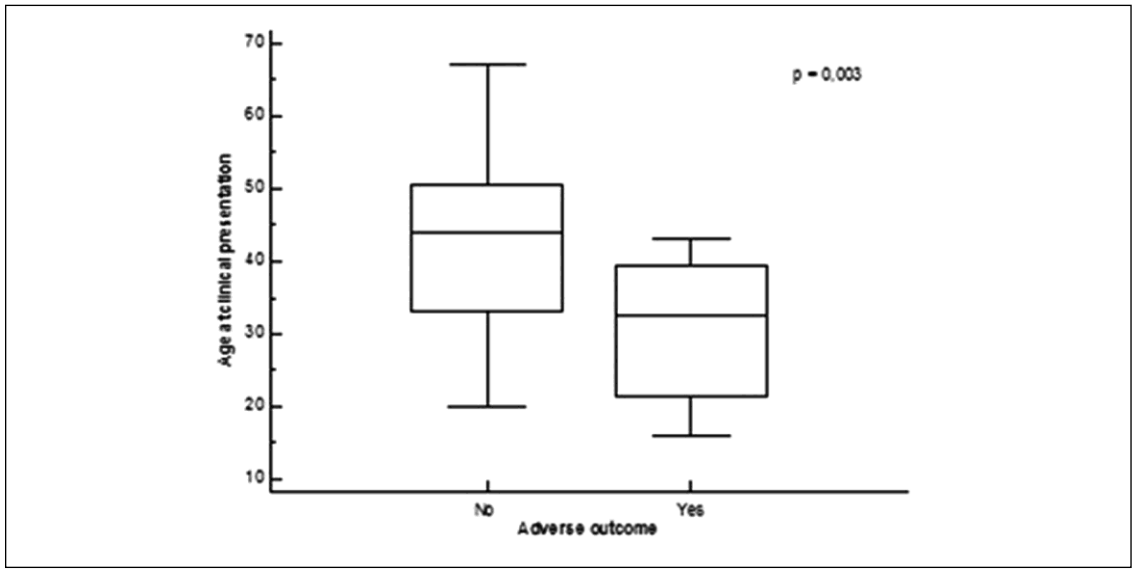


Figure 3.—Boxplots of age at presentation in the group with and without adverse outcome. (The central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The vertical line extends from the minimum to the maximum value).

Table II.—*Pathological findings of 19 heart analyzed.*

| Pathologic findings | Mean or % |
|---|---|
| Heart weight | 370±66.5 g |
| RV aneurysm | 26 |
| – Outflow tract | 16 |
| – Inflow tract | 5 |
| – Apex | 5 |
| RV involvement | |
| – Diffuse | 58 |
| – Regional | 42 |
| LV involvement | 32 |
| IVS involvement | 11 |
| RV thickness | 2.88±1.45 mm |
| – Reduced | 74 |
| – Increased | 26 |
| RV atrophy | |
| – Fibrofatty | 42 |
| – Fatty | 58 |
| Interface between survival and degenerative myocardium | |
| – Infiltrative pattern | 26 |
| – Cardiomyopathic pattern | 74 |
| Myocardial inflammation | 26 |

All hearts showed severe and transmural RV muscle loss, with varying degrees of extent and distribution, associated with fatty or fibrofatty replacement (Figure 4A). Atrophy of RV musculature was regional in 11 cases (58%; more frequently in the outflow tract and apex) and widespread in the remaining 8 cases (42%). Global mild-severe RV dilatation was seen in 6 cases (31.5%) and in the other cases RV dimensions were normal (13 cases; 68.5%). RV free wall thickness was increased in 5 cases (26%) and disclosed a variable degree of thinning in the remaining 14 cases (74%), with areas so thin as to appear completely devoid of muscle at transillumination (Figure 4B). LV involvement was diagnosed at gross examination in 6 hearts (32%), with aneurismal dilatation regarding LV free wall. In 2 cases (11%) we found an involvement of interventricular septum (IVS).

### Histologic findings

Histologic examination revealed severe and transmural loss of RV myocardium in all hearts specimens with residual myocytes < 60% by morphometric analysis (Figure 4C, D). According to gross inspection, microscopic lesions diffusely affected the RV free wall from the subepicardial to the subendocardial layer, with fatty (11 cases; 58%) or fibrofatty (8 cases; 42%) replacement.

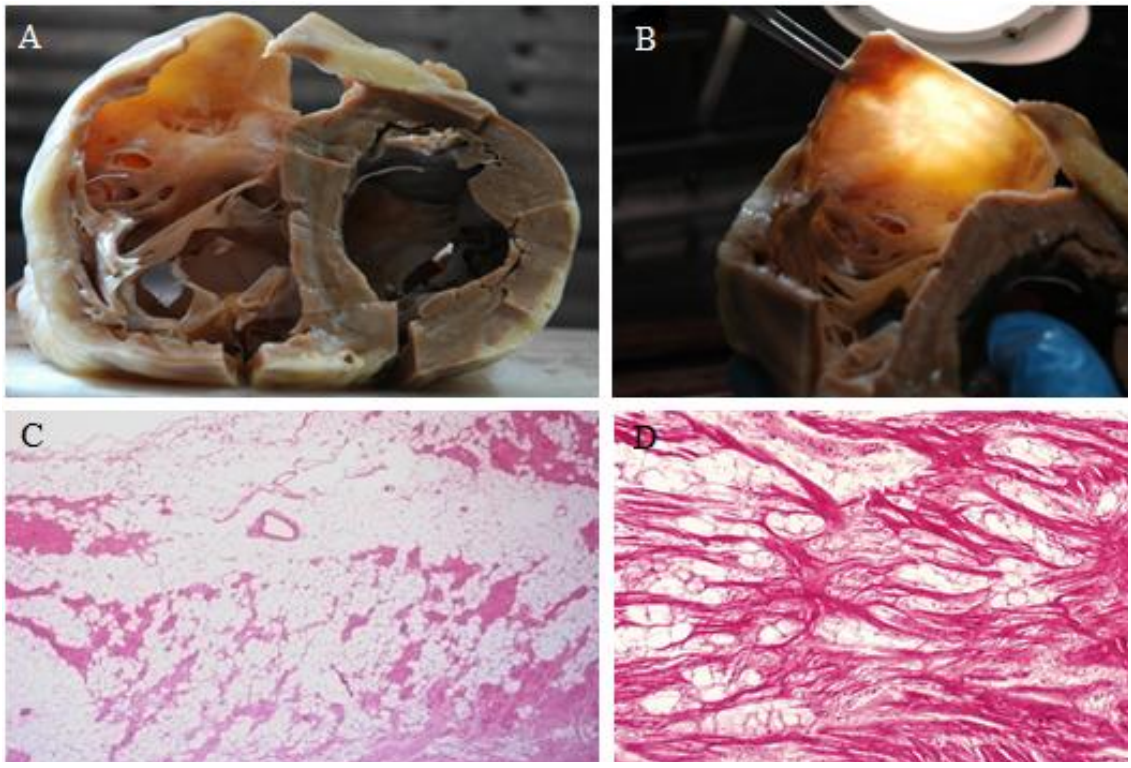


Figure 4.—Gross specimens of the examined heart at necropsy. (A) Note the massive RV with extensive fat that replace entire RV epicardium, and a thin free wall as to appear completely devoid of muscle at transillumination (B). Histopathologic (hematoxylin-eosin; x250) images show a transmural fatty (C) and fibrofatty (D) replacement with scatterd survival myocardium.

Surviving myocaridum with degenerative changes and atrophy was observed in a thin subendocardial layer, the trabeculae and scattered in areas with fatty or fibrofatty replacement. Myocytes showed degenerative changes, myocytolysis, necrosis and apoptosis (Figure 5A). Multifocal inflammatory infiltrates (active myocarditis) were seen in

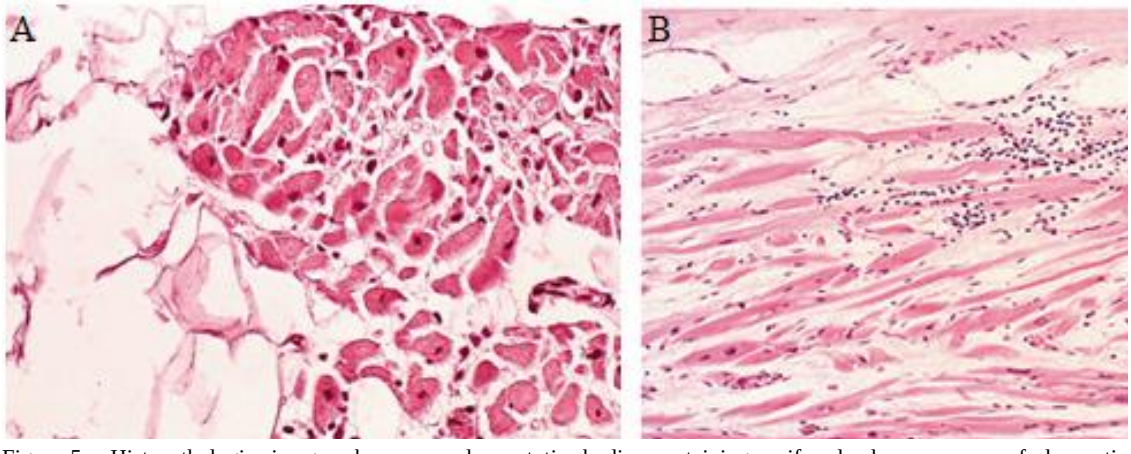


Figure 5.—Histopathologic images show several apoptotic bodies containing uniformly dense masses of chromatin, indicating apoptotic process (A), and multifocal inflammatory infiltrates (active myocarditis) (B) (hematoxylin-eosin; x250).

5 cases (26%). Infiltrates consisted of scattered interstitial collections of mononuclear cells close to necrotic or degenerative myocytes (Figure 5B).

The damage of conduction tissue was observed in the two cases with interventricular septum involvement, showing a fibrofatty replacement of hissian bifurcation. Analysis of the areas dividing survival myocardium from degenerative tissue, showed 2 different morphologic patterns: infiltrative (with irregular and blending interface) in 5 cases (26%), and cardiomyopathic (with a linear and regular interface) in 14 cases (74%). Infiltrative pattern presented the following features: increased RV free wall, fatty replacement, RV involvement only, absence of inflammatory infiltrates. Cardiomyopathic pattern showed a thin RV free wall (with aneurismal dilatation in 4 cases; 21%), fatty or fibrofatty replacement (32% and 42% respectively), inflammatory infiltrates and LV involvement.

Finally two patients of the living group underwent endomyocardial biopsy of the septum and the free wall of the RV for a better diagnostic approach of the disease. Both of them revealed myocyte loss (with residual myocytes < 60%), fibrofatty replacement and in one case inflammatory infiltrates. These data confirmed the diagnosis of ARVD/C.\1\2

## Discussion

Our study analyzed the main clinical and anatomical features of ARVD/C, a rare cardiomyopathy frequent cause of sudden death especially in young and athletes.[10, 11] Baseline clinical characteristics of our study population are similar to data reported in literature,[12, 13] with a prevalence in male sex and an age presentation during the second to fifth decade of life. We observed an important rate of death related to ARVD/C and interestingly no patients of the sudden death group had a family history of the disease, justifying the difficulty to achieve an early diagnosis in asymptomatic patients before death. Our data shows an association between death and the age presentation of the disease. It can be explained with a strict genetic basis characterizing young patients that usually onset with life-threatening arrhythmias. Many studies showed as juvenile form of ARVD/C presents an adverse outcome,[14] and the only way to avoid lethal events is represented by genetic screening, to identify patients with high risk, and exercise restriction. Clinical and genetic studies revealed that physical exercise increase the risk of sudden death in people with ARVD/C by five-fold [15,16]. Even our study confirmed an association between sport activity and risk of death. Excessive mechanical stress, such as during competitive sport activity and training, can aggravate the underlying dysplastic lesions and accelerate disease progression. For this reason we consider reasonable the exercise restriction recommended by clinicians for therapeutic management in patients with ARVD/C.[17] According to this a lifesaving strategy is the detection of symptom-free individuals at preparticipation screening for sport eligibility.

Instead of high mortality rate in our population, we observed a survival rate of 100% during follow-up in patients with a correct and early diagnosis of ARVD/C. Only few cases presented arrhythmic relapses or refractory heart failure thus requiring cardiac transplantation. Many studies tried to identify long-term prognostic predictors of adverse outcome in this patients.[18, 19] We considered patients with adverse outcome in term of sudden death, refractory heart failure and heart transplantation. Our results revealed that biventricular involvement and early age presentation of the disease have an incremental power in predicting adverse outcome. Biventricular involvement underlies an important widespread and progression of ARVD/C thus alterating ventricular function. As previously reported even an early age presentation shows an important risk not only in term of death but of adverse outcome. Pathologic findings revealed different anatomic features of ARVD/C with special references to LV involvement, inflammatory infiltrates and apoptotic proc-

ess. Many authors agree with the adoption of the broad term "arrhythmogenic cardiomyopathy" [3] due to the description of the frequent involvement of LV ventricle and left-dominant form of ARVD/C.[4] In our experience LV involvement was observed in 32% of cases in the second group, and in 17% of cases in the first group. As described in previous studies,[20] we observed 3 main form of ARVD/C: classic with main RV involvement, left dominant with main LV involvement and biventricular with an involvement of both ventricles. Our findings showed other two important features of ARVD/C: inflammatory infiltrates and apoptotic process. Although it is not clear whether inflammation in ARVC is a primary event or a reaction to spontaneous necrosis, inflammatory infiltrates are an histopathologic marker of an ongoing myocardial damage that suggests a progressing myocardial disease.[21] Moreover apoptosis has recently been shown to be a mode of myocyte death in ARVC and might provide a unifying explanation for progressive myocardial loss.[22] These changes are frequent in ARVD/C and probably play a major part in triggering life-threatening arrhythmias. We finally report the recognition in 2 cases of fatty replacement regarding hissian bifurcation as possible agents able to trigger lethal arrhythmias. There are some limitations to consider when interpreting the result of this study. A prospective, randomized study design is difficult to perform in patients with ARVD/C because of the relatively low disease prevalence. The study design was that of an observational survey of 6 collaborative medical centers, with potential limitations in patients selection. Although written informed consent was acquired prospectively, all clinical and demographic data were collected retrospectively. This might be a source for recall bias. Moreover, since the study was not prospectively performed, results from the direct comparison between data of living and autopsy subjects should be interpreted with caution. Finally our study is based on a small sample size. However, this is a rare disease and our inclusion criteria were very strictly, including only patients with definite diagnosis of ARVD/C in order to enhance the specificity of our results. Our purpose is to extent in the future our study population in order to collect a complete registry of entire Sicily.

## Conclusions

Arrhythmogenic Right Ventrticular Dysplasia/Cardiomyopathy is an unusual condition with a variable clinical presentation. Our study confirms a previous report by Corrado *et al.*,[23] which identify 3 main clinical form of ARVD/C: a silent phase with concealed abnormalities and sudden death might be the first manifestation, an overt right ventricular electrical phase and an end-stage with right ventricular or biventricular failure. Actually the spectrum of our study population ranges from concealed RV changes detected at autopsy in previously asymptomatic young patients to biventricular cardiomyopathy with severe pump failure. Moreover we find that biventricular involvement, early age at presentation, physical exercise represent predictors that play an important role in terms of progression and adverse outcome of ARVD/C. However to this day is often difficult precociously identify silent form of ARVD/C that frequently lead to life-threatening arrhythmias.

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