

## Original Article

# Pathological observations and tissue quantitative assessment of Han Chinese sudden deaths caused by arrhythmogenic right ventricular cardiomyopathy: a case-control study

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**Abstract:** Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty or fatty infiltration of heart muscle. We compared the pathological lesions of patients with sudden death from ARVC and controls with sudden death from other diseases. Methods and results: From 1999 to 2014, eight sudden deaths were ascribed to ARVC at the Department of Forensic Medicine, Tongji Medical College, Huazhong University of Science and Technology. There were six females (75%; 26-57 years old; average 46.3±10.8 years) and two males (25%; 23-46 years old; average 34.5±16.3 years). Most deaths (75%) occurred between 40 and 60 years of age. The deaths occurred during work (37.5%), sleep (37.5%), childbirth (12.5%), and emotional stress (12.5%). One patient (12.5%) had a history of syncopal episodes. The heart weight was 415.0±106.2 g, and 75% had cardiomegaly. The left ventricular (LV) thickness was 13.8±2.5 mm, and 50% had LV hypertrophy. The right ventricular (RV) thickness was 3.4±1.4 mm. Most lesions (75%) were restricted to the right ventricle, with biventricular subtype in the remaining lesions. Chamber enlargement was seen in 87.5% patients. Fatty pattern was seen in 75%, and fibrofatty pattern was seen in 25%. Transmural infiltration was seen in 25% of patients. Fatty tissue infiltration was also seen in the sinoatrial and atrioventricular nodes and His bundle. Residual myocytes were lesser and fatty tissue was greater in the RV midzone compared with that of the controls. Conclusion: Fatty infiltration limited to the RV was seen in most patients who died with ARVC. Midzonal area appears to be better than the epicardium and endocardium for assessing the histological changes of ARVC.

**Keywords:** Cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), sudden death

## Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary disorder characterized by replacement of myocytes with adipose and fibrosis tissues [1]. ARVC was first described as “De Motu Cordis et Aneurysmatibus” by Giovanni Maria Lancisi in 1736 [2]. It was initially described as ventricular tachyarrhythmias with left bundle branch block morphology in 1982 [3]. The epsilon wave of the disease was described in 1984 [4]. ARVC was initially believed to result from defective embryonic development that led to right ventricular dysplasia. Therefore, it was called arrhythmogenic right ventricular dysplasia [3, 5]. It is now known that ARVC is inherited in at least 50% of the

cases and is typically transmitted as an autosomal dominant trait with variable penetrance [6].

The clinicopathological patterns of ARVC are highly variable, ranging from no symptoms to ventricular tachycardia, right heart failure, and biventricular heart failure. ARVC may predominantly affect right ventricular, left ventricular, or bi-ventricular. The prevalence of ARVC is estimated to be between 1:1000 to 1:5000 [7, 8]. Exercise is a possible trigger for ARVC death [9], and ARVC contributes to almost 25% of sudden deaths in victims aged <30 years [10].

The pathological changes of ARVC in patients with sudden death in the Han population are unknown. We report the results of comparison

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**Table 1.** Basic characteristics of ARVC victims

Case number	Gender/ Age	Occupation	Circumstances	Symptoms
1	M/23	Individual businessman	Driving	Syncope
2	M/46	Carpenter	Work	-
3	F/26	Teacher	Childbirth	-
4	F/44	Food company worker	Quarrelling	-
5	F/49	Accountant	Sleep	-
6	F/50	Farmer	Sleep	-
7	F/52	Farmer	Work	-
8	F/57	Farmer	Sleep	-

of pathological and quantification analyses of all slices between 8 cases of ARVC and 23 cases of control groups.

### Materials and methods

#### Study population and groups

Eight patients with sudden death due to ARVC were selected from the files of 5106 patients in our department who presented between January 1999 and December 2014. The cause of death for each victim was identified based on the autopsy findings, histological examinations, and toxicology analyses. Twenty-three patients were selected as controls. Of the controls, eight had dilated cardiomyopathy (DCM, control group I), eight had hypertrophy cardiomyopathy (HCM, control group II), and seven had non-cardiac causes of sudden deaths (Control group III).

#### Macroscopic and microscopic examinations

Samples were taken from the affected anterior walls of the left and right ventricles. The slides were stained with both hematoxylin & eosin (H & E) and Masson trichrome to differentiate between fibrous and cardiac tissues. A slide scanner Zeiss Axio Scan Z1 (Carlzeiss Macroscopy GmbH, Germany) was used to scan the slides. The slides stained with Masson trichrome were scanned by  $\times 40$  at 100%. Image-Pro-Plus Version 6.0 (Media Cybernetics) was used to calculate the areas of the heart muscle, fibrous, and fatty tissue [11]. The left and right ventricles were divided into epicardium, mid-zone, and endocardium. The diagnosis of ARVC was confirmed by the presence of gross or histological evidence of regional or diffuse transmural fibro-fatty infiltration of the right ventricu-

lar free wall reaching the endocardium in the absence of valve, coronary, and pericardial disease [12].

#### Statistical analysis

Statistical analyses were conducted by SPSS 20.0 (for windows). Continuous data were presented as mean  $\pm$  standard deviation, and categorical data were presented as number and/or percentage. Independent

student's t-test was performed for continuous data. A 2-tailed  $p$ -value  $<0.05$  was considered statistically significant.

#### Ethical approval

All parts of the study were approved by the Institutional Ethical Committee of the Department of Forensic Medicine, Tongji Medical College, Huazhong University of Science and Technology. Informed consent was obtained from the families/surrogates of all participants according to the Declaration of Helsinki.

### Results

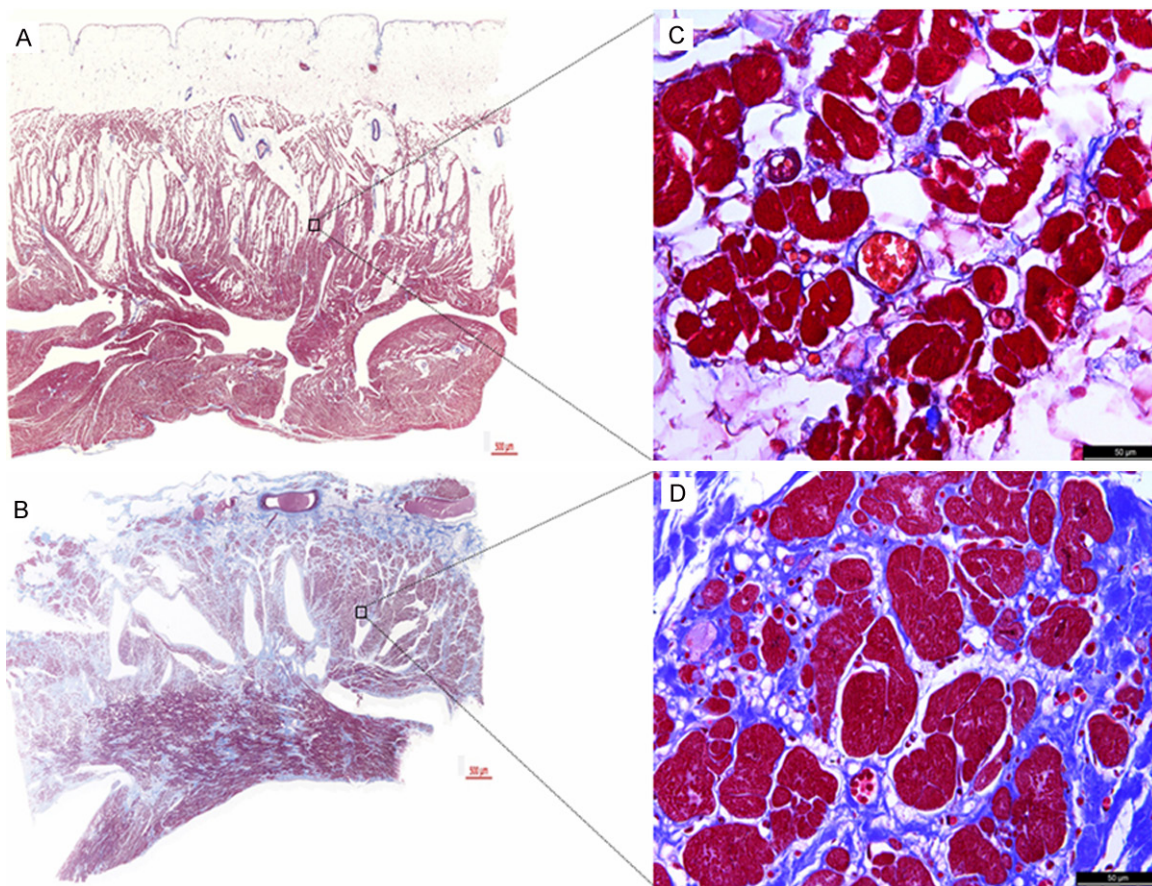
#### Basic characteristics of sudden deaths caused by ARVC

Between 1999 and 2014, 5106 patients were diagnosed with ARVC at our department, of which eight had a sudden death (rate = 0.16%). These patients consisted of two males (25%; 23-46 years old; average  $34.5 \pm 16.3$  years) and six females (75%; 26-57 years old; average  $46.3 \pm 10.8$  years). As shown in **Table 1**, 75% (6 cases) of deaths occurred at ages between 40 and 60 years. Two males died while working (25%), one female died while working (12.5%), three females died while sleeping (37.5%), one female died during childbirth (12.5%), and one died when quarreling with others. Only one patient (12.5%) had a history of syncopal episodes.

#### Pathological examinations

The control hearts had patent coronary arteries. None of them showed transmural fatty or fibrofatty infiltration. The fatty tissue in the left

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**Figure 1.** Representative microscopic images. A. Scan microscopy of right ventricular free wall showing a deposit and islands of residual myocytes in patients with fatty accumulation restricted to the right ventricular wall (Masson Trichrome Stain). B. Scan slice microscopy of left ventricular free wall showing massive fibrofatty infiltration around the residual myocytes in patients with fibrofatty biventricular ventricular walls (Masson Trichrome Stain). C. High magnification microscopy showing adipose infiltration (Masson Trichrome Stain, original magnification,  $\times 400$ ). D. High magnification microscopy showing fibrofatty accumulation (Masson Trichrome Stain, original magnification,  $\times 400$ ).

and right ventricles in the control hearts was limited to the sub-epicardium or the outer third of the myocardium. Macroscopically, all cases of group I and II had cardiomegaly (heart weight  $>400$  g in men and  $>350$  g in women). Chamber enlargement was seen in all cases of group I, and left ventricular hypertrophy was seen in all cases of group II. Microscopically, intestinal fibrosis was observed in groups I and II.

Microscopically, six patients with ARVC (75%) showed right ventricular predominance. Their lesions extended into the right ventricular anterior wall and apex. The other two patients showed the bio-ventricular type. The mean heart weight was  $415.0 \pm 106.2$  g, and 75% of the patients (4 women and 2 men) had cardiomegaly. The mean left ventricular (LV)

thickness was  $13.8 \pm 2.5$  mm. Four patients (3 women and 1 man, 50% of all cases) showed LV hypertrophy. The mean right ventricular (RV) thickness was  $3.4 \pm 1.4$  mm and four patients (50%) had RV dilation. Two patients (25%) had bio-ventricular dilation and one (12.5%) had LV dilation. The degree of coronary artery stenosis was  $<25\%$  in two patients, whereas the others had normal coronary arteries.

Microscopically, 75% of the patients (6 patients) had a fatty type (Figure 1A and 1C), and 25% (2 patients) had a fibrofatty type appearance (Figure 1B and 1D). The sub-epicardium and endocardium either were joined by the sides or had clusters of trapped myocytes separated by fatty/fibroadipose tissue (including the lipid-

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**Table 2.** Demographic data and histomorphometric results

	ARVC	Control group I	Control group II	Control group III	P value*
Gender (M/F)	2/6	3/5	5/3	4/3	0.240
Age (Mean ± SD)	43.3±12.3	36.6±16.7	46.0±16.0	34.7±10.8	0.470
LV total area					
Myocardium	57.7±29.5	73.0±7.5	55.2±26.7	70.3±28.4	0.462
Fibrosis	14.8±16.5	12.0±6.1	30.0±32.2	7.3±5.0	0.904
Fat	27.5±22.0	14.8±6.2	15.2±8.9	22.1±30.9	0.295
LV epicardium					
Myocardium	24.2±19.9	52.3±25.9	46.8±22.9	11.6±12.4	0.391
Fibrosis	22.5±10.8	17.2±11.3	31.5±20.8	12.4±5.4	0.709
Fat	50.0±26.6	30.8±27.9	21.3±13.7	76.1±13.3	0.701
LV midzone					
Myocardium	65.5±36.0	74.8±14.3	56.2±28.9	74.3±30.1	0.810
Fibrosis	9.7±17.8	17.0±13.6	28.5±33.3	7.1±5.9	0.454
Fat	24.8±27.0	8.2±6.4	15.3±10.5	18.6±32.9	0.318
LV endocardium					
Myocardium	61.7±23.8	62.2±19.8	62.3±27.1	80.4±12.7	0.482
Fibrosis	23.7±21.4	13.8±8.2	25.3±22.8	8.1±5.9	0.299
Fat	14.5±20.5	24.0±13.1	12.5±13.4	11.6±8.0	0.851
RV total area					
Myocardium	23.8±16.3	42.2±16.2	46.4±19.8	56.4±14.3	0.001**
Fibrosis	7.3±3.2	19.2±13.6	18.3±7.9	49.3±67.7	0.359
Fat	68.3±15.3	58.7±24.8	35.5±18.4	18.7±10.4	0.001**
RV epicardium					
Myocardium	8.3±7.3	1.5±1.6	6.0±7.3	19.7±21.4	0.512
Fibrosis	17.5±14.4	25.5±25.1	22.9±19.5	30.6±19.3	0.049**
Fat	74.3±19.1	72.7±26.6	71.1±22.6	49.6±30.8	0.062
RV midzone					
Myocardium	21.8±14.2	54.5±20.4	50.5±20.7	61.3±16.4	0.015**
Fibrosis	3.0±2.0	13.3±9.3	15.9±9.2	22.0±17.5	0.053
Fat	75.5±14.9	32.0±26.6	33.5±22.8	16.9±9.0	0.002**
RV endocardium					
Myocardium	34.5±30.0	47.0±23.3	57.1±28.6	64.1±21.5	0.018**
Fibrosis	29.5±27.0	24.3±15.6	28.5±28.7	26.3±23.2	0.122
Fat	36.0±29.8	28.5±29.2	14.5±4.7	9.3±6.5	0.220

\*P value: ARVC group compared with the total control groups (I, II and III). Control group I: dilated cardiomyopathy, II: hypertrophy cardiomyopathy, III: non-cardiac deaths. \*\*P value <0.05.

rich sarcoplasmic vacuoles of myocytes). Two patients (25%) had biventricular fibrofatty changes with inflammatory mononuclear cell infiltrates (more than 10 cells per focus) or diffuse interstitial fibrosis. Two patients (25%) had anomalies of the cardiac conduction system: one patient had fatty tissue infiltration of the sinoatrial node (SAN), His bundle (HB), and atrioventricular node (AVN) fatty tissue infiltration; the other had fatty infiltration in the HB and AVN.

### *Quantification of fibrosis, fatty tissue, and muscle contents in ARVC*

Compared with the non-ARVC group, the ARVC group had no difference in the LV free wall, fibrosis, fatty tissues, or muscle contents, irrespective of the area calculated ( $P>0.05$ ).

In the RV mid-zone, there was a greater percentage of fat and lower percentage of myocytes compared with the controls ( $P<0.05$ ). Patients with ARVC had lesser myocytes in the

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RV endocardium and a lower fat content in the RV epicardium compared with the controls (Table 2).

### Discussion

In this study, all deaths occurred during sleeping or activities of daily living. Most (75%) patients died between the ages of 40 and 60 years. These data confirm that ARVC may cause deaths in young athletes during sports or even during activities of daily life, including sleep [13].

The clinical and pathological phenotypes of ARVC vary considerably. The “silent stage” of the disease is characterized by ventricular tachyarrhythmia in the setting of well-preserved morphology, histology, and ventricular function. “Overt electrical heart disorder” is characterized by underlying severe symptomatic ventricular arrhythmia. “RV failure” is characterized by myocardial replacement in the RV, leading to RV failure. “Biventricular failure” is characterized by the progression of RV and LV dysfunction, and is usually the final phase of the natural history of ARVC [14]. Sudden death in ARVC may occur at any stage. ARVC victims died under different circumstances in our study, including 37.5% of the deaths that occurred during work that may involve increased sympathetic activity [15]. However, 37.5% of the deaths occurred during sleep. A possible explanation is increased vagal activity and withdrawal of sympathetic activity that may have an arrhythmogenic effect [16]. Pregnant women are at an increased risk of ventricular arrhythmias in the last trimester. Additionally, one victim died during emotional stress, which triggered a ventricular arrhythmia. In this study, 12.5% of patients presented with syncopal episodes prior to death. This is in consistency with the previous clinical reports where syncope has been reported to be one of the common clinical symptoms of ARVC [17].

In this study, 75% patients showed RV predominance, with the remaining showing bi-ventricular subtypes. The lesions were seen in the right atrium in 12.5% patients. In spite of predominantly involving the RV, the lesions of ARVC also extended to other structures of the heart, particularly the left ventricle and atrium. Most patients (75%) had cardiomegaly (including LVH). The heart weights were seen to be 100%

above 400 g in a previous study [18]. In a different study, 14.5% of patients with ARVC had LVH [19]. Therefore, cardiomegaly (including LVH) may play a role in ARVC deaths. Fatty infiltration most commonly involved RV (75%). A previous study showed the fatty or fibrofatty infiltration limited to RV was associated with a higher risk of death [19]. Therefore, the relationship between structural abnormalities and sudden death needs further research.

Ventricular tachycardia and fibrillation appear to be responsible for sudden deaths in asymptomatic youngsters and athletes with ARVC [20-22]. Fatty or fibrofatty infiltration of myocardium, which transforms the compact myocardium into lace-like strands of residual myocytes, may provide the anatomic substrate for arrhythmias [23]. A previous study showed that anomalies of the conductive tissue may be responsible for some ARVC deaths. In this study, 25% of the patients had abnormal cardiac conduction system [19]. Furthermore, life-threatening ventricular arrhythmias often occur in the concealed phase of the disease before the onset of structural changes. The loss of desmosome integrity is thought to facilitate arrhythmias [24]. The substrate for arrhythmias in ARVC should be further investigated.

There are three hypotheses for myocyte loss in ARVC: degeneration, inflammation, and trans-differentiation. The degenerative hypothesis proposed that myocytes are lost due to an inherited metabolic or ultrastructural defect. The inflammatory hypothesis suggests inflammation as the basis of myocyte loss. The prevalence of inflammation varies widely in different studies, ranging from 5.5% in a previous study to 25% in the present report. A previous study concluded that inflammation is not a cause of ARVC but rather an aggravating factor [19]. Another study found that inflammation was rarely seen in the fatty variant of ARVC [25]. It appears that inflammatory infiltrates are not seen in all cases of ARVC. The trans-differentiation hypothesis proposes that cardiac myocytes undergo a switch to adipose tissue. The residual myocytes show partial replacement of myofibers with the lipid-rich sarcoplasmic vacuoles, as also observed in the present study. This may represent a form of lipid metaplasia, and may be a precursor to the presence of more abundant areas of fat replacement [26].

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In the normal adult heart, epicardial fat is distributed in the atrio-ventricular and inter-ventricular grooves, along the major branches of coronary arteries, over the free wall of RV, and over the apex of LV. A previous study showed that fat predominated in the epicardial layer in the right and left free walls in ARVC [18]. However, in this study, fat tissue was seen in the midzone layer of ARVC patients rather than epicardial and endocardial layers. In ARVC patients, normal and pathological epicardial fatty tissue was difficult to differentiate in the ventricular free wall. Previous studies, however, documented that the epicardial wall could be destroyed by adipose tissues. Endomyocardial biopsy from the right septal ventricular wall may help diagnose ARVC. This tissue is often taken from the endocardium and midzone. In this study, RV epicardium had less fibrosis and RV endocardium had less muscle compared with the controls. The RV midzonal area had less muscle and more fat than controls.

### Conclusion

Sudden death in ARVC most commonly occurs in asymptomatic patients during sleep and non-strenuous activities. Fatty replacement limited to the RV is commonly seen in patients with sudden deaths. The midzone appears to be better suited for constitution content analysis compared with the epicardium or endocardium.

### Disclosure of conflict of interest

None.

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