Clinico-radiological profile of arrhythmogenic right ventricular dysplasia at a tertiary care center: Two year experience

Feroze Shaheen a, Khurshid Iqbal b, Imran Hafeez b, Naseer.A. Choh a, Nisar A Tramboo b, Ajaz Lone b, Shamim Iqbal b, Wasim Ahmed b, Amit Gupta b

a Department of Radiology, Shere-Kashmir-Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K 190 011
b Department of Cardiology, Shere-Kashmir-Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K 190 011
a–b India

Background: Arrhythmogenic right ventricular dysplasia (ARVD/C) refers to fibro fatty infiltration replacement of ventricular myocardium especially that of right ventricle. The clinical presentation varies from asymptomatic state to ventricular tachycardia, heart failure and even sudden death. Diagnosis is established using modified ARVD/C taskforce criteria. Among all the various modalities of diagnosis, magnetic resonance imaging (MRI) gives most comprehensive evaluation of both morphological and functional abnormalities in this disease. MRI may not only obviate need for myocardial biopsy but also give insights into the nature of disease like presence of left ventricular myocardial involvement. We present our 2 years experience of ARVD/C patients who were admitted in our center and in whom diagnosis of ARVD/C was supported by excellent MR imaging.

Materials and methods: This study was conducted by Department of Radiology and Cardiology SKIMS, a tertiary care center for a period of 2 years. Patients with suspected ARVD/C based on clinical, electrophysiological and echo-cardiographic findings were subjected to MR imaging. Patients were excluded if they had history metallic implants, claustrophobia or were uncooperative. In this study stress was laid on diagnostic role of MRI in ARVD/C.

Results: The median age at presentation was 31 years (range 21–43 years). 80% of patients were males. Most common clinical presentation was palpitations (40%). Syncope was present in 27% and heart failure in 13%. EKG suggestive of ARVD was seen in 87%. Echocardiographic features suggestive of ARVD/C was seen in all 15 patients. Family history of premature sudden death less than 35 years old was present in one patient only. MRI evidence classical for ARVD/C was seen in 80%.

Conclusion: Demographic features and mode of presentation of our patients is consistent with what has been rest of the world. We performed MRI in all patients to increase the specificity of our diagnosis. MR imaging allows a three-dimensional evaluation of the right ventricle and provides the most important anatomic, functional, and morphologic criteria for diagnosis of ARVD/C within one single study. MR imaging appears to be the optimal imaging technique for detection and follow-up of clinically suspected ARVD/C.

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Corresponding author.
E-mail addresses: shaheenfp64@rediffmail.com (F. Shaheen), Iqbal.khurshid@gmail.com (K. Iqbal), imihaf@gmail.com (I. Hafeez), naseerchoh@rediffmail.com (Naseer A. Choh), dnisaratramboo@gmail.com (N.A Tramboo), drajaz66@yahoo.com (A. Lone), drshamimiqbal@gmail.com (S. Iqbal), wasim.skims@gmail.com (W. Ahmed), amitcardio12@gmail.com (A. Gupta).

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Introduction

ARVD/C is a cardiomyopathy of unknown etiology characterized by structural and functional abnormalities of right ventricle leading to ventricular arrhythmias and progressive right heart failure. It presents in sporadic and familial forms and has an overall prevalence of 1:5000 in USA. Annual death rate from ARVD/C is estimated to be 2.5% [1]. The disease is recognized as a major cause of death in young adolescents and in one series it accounted for 20% of sudden death in all individuals younger than 35 years and 22% deaths in young athletes [2]. Underlying pathological substrate of ARVD/C is myocyte loss with fibro fatty replacement of ventricular myocardium, focal thinning of right ventricular myocardium resulting in global or regional contraction abnormalities. Defective desmosomal proteins are the presumed cause of majority of familial cases of ARVD/C but not proven for sporadic cases without genetic origin. Although most cases of familial origin are autosomal dominant with mutations affecting components of cardiac desmosomal proteins resulting in disruption of cell to cell adhesions and myocyte loss, the clinical manifestations are variable ranging from complete lack of symptoms to severe disease. This variable expressivity of the disease may be due to variable penetrance or other associated unknown causes [3]. The diagnosis of ARVD/C is based on the structural, histologic, electrocardiographic, arrhythmic, and genetic factors proposed by ARVD/C task force in 1994 [4]. Modified task force criteria was proposed in 2010 [5]. The criteria have been modified to incorporate new knowledge and technology to improve diagnostic sensitivity but with the important requisite of maintaining diagnostic specificity. Negative T waves in lead V1–V3 and ARVD/C in first degree relative were reclassified as major criteria; negative T waves in V1–V2 or V4–V6, negative T waves in V1–V4 with right bundle branch, terminal activation duration (TAD) OF QRS ≥ 55 ms in V1–V3, VT of left bundle branch morphology with superior axis and pathogenic mutation associated with ARVD/C are newly introduced criteria; late potentials by SAEG in at least one of the three parameters and over >500 premature ventricular complexes/24 h on holter are adaptations; quantification of RV structural abnormalities and dysfunction and tissue characterization by RV biopsy [6]. Magnetic resonance imaging (MRI) allows multiplanar evaluation of the right ventricle (RV), enabling accurate morphologic and functional assessment without any geometric assumptions [7]. Intramyocardial fat accumulation is a pathologic hallmark of ARVD/C, and MRI has excellent tissue characterization capability, particularly for fatty tissue [8–10]. The ability to provide tissue characterization as well as to visualize RV function makes MRI suitable for follow-up of patients and to study the progression of disease (see Figs. 1 and 2).

Materials and methods

This study was conducted by Department of Radiology and Cardiology SKIMS, a tertiary care center for a period of 2 years from 2009 to 2011. Patients with suspected ARVD/C based on clinical, electrophysiological and echocardiographic findings were subjected to MR imaging (Magnetom Avanto, Siemens, Erlangen, Germany). Patients
were excluded if they had history metallic implants, claustrophobia or were uncooperative. In this study stress was laid on diagnostic role of MRI in ARVD/C. Following imaging techniques were used:

- TIW double inversion recovery black blood sequence in axial, RVOT and short axis planes followed by fat saturated TIW double inversion recovery in same planes using same slice thickness of 5 mm, slice gap 5 mm and FOV of 28 cm. Thickness of 8 mm, slice gap 2 mm and field of view (FOV) 36–40 cm using parallel imaging technique.
- Short axis steady state in free precession (SSFP) cine for functional assessment.
- Short axis, RVOT and LVOT planes for post contrast LGE imaging with myocardial nulling using slice thickness of 8 mm, slice gap 2 mm with phase sensitive inversion recovery sequence.

Right ventricular function analysis was done using Argus analysis software (Siemens Medical Solutions, Forchheim, Germany).

Dose of gadolinium used was 0.1 mmol/kg.

Results

During the period of 2 years 15 patients with suspected ARVD/C based on clinical, electrophysiological and echocardiographic findings were admitted in our institution. There demographic, clinical and diagnostic parameters are depicted in Table 1.

The median age at presentation was 31 years (range 21–43 years). 80% of patients were males (n = 12) and 20% were females (n = 2). Most common clinical presentation was palpitations (40%). Syncope was present in 27% and heart failure in 13%. 20% of our patients were asymptomatic in whom ARVD/C diagnosis was incidental finding. EKG suggestive of ARVD as per modified ARVD task force criteria (major or minor criteria) was seen in 87% (n = 13). The most common electrocardiographic feature was T-wave inversion in right precordial leads (80%) which is a major criteria as per modified task force criteria. Epsilon wave was seen in one patient. Documented ventricular tachycardia of LBBB morphology was seen in 20% (n = 3). Echocardiographic features suggestive of ARVD/C as per ARVD/C task force criteria (major or minor criteria) were seen in all 15 patients. All patients had RV Dyskinesis with RVOT dilatation which was important clue for further diagnostic evaluation of ARVC/D. RV aneurysms were seen in 26%. RVOT dimensions in PSAX > 36 mm was seen in 80% and <36 in 20%. Family history of premature sudden death less than 35 years old was present in one patient only. Three patients received ICD, two patients received it for secondary prevention and one
who had family history of sudden cardiac death received it for primary prevention. Five of our patients were admitted with recurrent heart failure during this period, four patients were lost on follow up and rest are following us in reasonably good state.

**MRI finding in our patients**

MRI evidence classical for ARVD/C was seen in 80% (n = 12). Following pattern was seen:

Three (20%) patients had fatty replacement of right ventricular apex and sub tricuspid region with normal right ventricular cavity with hypokinesis of the involved ventricular wall. Clinically all these patients had tachyarrhythmia with epsilon waves in one patient.

Fibro fatty replacement of most of right ventricular wall with post contrast enhancement, dilated right ventricular cavity and reduced right ventricular functions was seen in three (20%) patients.

Markedly thinned right ventricular wall with dilated right ventricular cavity, systolic a diastolic dysfunction (evaluated by MR velocity mapping across tricuspid valve) but no visible hyperintense signal in right ventricular wall on T1W sequence was seen in four (26%) patients.

Fibro fatty replacement of right ventricular wall with epicardial enhancement of most of right ventricular wall and IVS and part of left ventricle with systolic dysfunction of right ventricle with reduced ejection fraction was seen in two (14%) patients.

**Discussion**

ARVD/C results from fibro fatty replacement of the right ventricular wall which in turn leads to arrhythmogenicity and progressive right ventricular failure unless punctuated by sudden death due to arrhythmia. The cause of fatty or fibro fatty replacement of ventricular wall has been postulated on the basis of various genetic, pathologic, clinical and biochemical findings. In a large proportion of patients (30–80%) the disease is familial, primarily autosomal dominant with variable penetrance. Besides two autosomal recessive syndromic forms of ARVD namely Naxos disease and Carvajal syndrome have been discovered having 100% genetic penetrance [1]. The dominant form of disease shows polymorphic expressivity ranging from complete lack of symptoms to severe disease phenotype experiencing sudden death which has been attributed to modifier genes, environmental factors and gender effects [11]. The genetic mutations involve mainly the desmosomal proteins. The defective desmosomal proteins are thought to result in disruption of cell to cell adhesion causing myocyte detachment and apoptosis. The walls most affected would be those which are thinnest and have high mechanical stress like the right ventricular wall [3]. Pathologically two morphological variants are found: fatty and fibro fatty. The former shows complete replacement of myocardium without thinning of the wall and occurs exclusively in right ventricle whereas the latter shows thinning of right ventricular wall and part of left ventricular wall with fibro fatty replacement. Classically the right ventricular wall involvement occurs in what is known as triangle of dysplasia i.e. right ventricular sub tricuspid area, the apex and infundibulum [12].

The modified task force group on ARVD has established various criteria for the diagnosis of ARVD and divided them into major and minor criteria with either two major or one major and two minor criteria or four minor criteria being sufficient for the diagnosis of ARVD [5]. Classically the EKG shows regular sinus rhythm with QRS > 110 ms in VI, Epsilon wave just beyond QRS complex in VI and inversion of T waves in precordial leads from V1 to V3 or ventricular tachycardia of LBBB morphology [4]. 2D echocardiography reveals increase systolic and diastolic dimensions, hyperrefractile moderator band and apical aneurysms. Diastolic RVOT enlargement is usually more common. An RVOT dimension larger than 30 mm from PLAX view has highest sensitivity (89%) and specificity (86%) for diagnosis of ARVD/C [13]. Although myocardial biopsy

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**Table 1. Demographic features and mode of presentation.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Male (M)</th>
<th>Female (F)</th>
<th>Age in years</th>
<th>Predominant presentation</th>
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<tr>
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<td>F</td>
<td>28</td>
<td>Syncope</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td></td>
<td>36</td>
<td>Palpitations</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td></td>
<td>33</td>
<td>Palpitations</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td></td>
<td>41</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td></td>
<td>21</td>
<td>Syncope</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td></td>
<td>29</td>
<td>Palpitations</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td></td>
<td>27</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td></td>
<td>32</td>
<td>Syncope</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td></td>
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<td>Syncope</td>
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<tr>
<td>10</td>
<td>M</td>
<td></td>
<td>29</td>
<td>Palpitations</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td></td>
<td>40</td>
<td>Heart failure</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td></td>
<td>25</td>
<td>Palpitations</td>
</tr>
<tr>
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<td>Asymptomatic</td>
</tr>
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<tr>
<td>15</td>
<td>M</td>
<td></td>
<td>31</td>
<td>Palpitations</td>
</tr>
</tbody>
</table>

M, Male; F, Female.
would be the standard reference for diagnosis, it lacks sufficient sensitivity owing to segmental nature of disease. Even when biopsy is obtained from right ventricular free wall, sensitivity is only 67% based on the criteria of >3% fat and less than 40% fibrous tissue replacing myocardial muscle [14]. Significant fatty replacement of the right ventricle occurs in >50% of normal hearts in elderly people and a degree of intramyocardial fat in the anterior apex of right ventricle existed in 15% of controls [15,16].

Magnetic resonance imaging has been used for evaluation of ARVD/C for quite some time now and has proved to be a robust and comprehensive investigation tool.

The typical criteria that can be demonstrated with MR imaging of ARVD/C are [17].

(A). Major:
1. Fatty infiltration of right ventricular myocardium with high signal intensity on T1W.
2. Fibro fatty replacement leading to diffuse thinning of right ventricular myocardium.
3. Aneurysm of right ventricle and right ventricular outflow tract.
4. Severe dilatation of right ventricle and right ventricular outflow tract.
5. Global systolic dysfunction.

(B). Minor:
1. Mild dilatation of right ventricle and right ventricular outflow tract.
2. Regional contraction abnormalities.
3. Global diastolic dysfunction.

Our patients presented somewhere between second decade to fifth decade, the youngest patient was 21 years old and oldest patient was 43 years old. This is consistent with the world literature [18,19]. In one of the largest cohort of ARVD/C, patients typically presented between the second and fifth decades of life. Although only eight patients presented before the onset of adolescence or after 50 years of age, the age at presentation ranged widely between 2 and 70 years. The marked variability in age of presentation suggests that ARVD remains concealed for varying periods of time in different individuals [19]. In our patients there was wide spectrum of presentation from asymptomatic state to ventricular tachycardia, syncope and heart failure which is consistent with world literature. Palpatation was most common symptom as seen in other studies also [19]. In our patients EKG and echocardiographic features supported diagnosis of ARVD/C as per modified ARVD/C task force criteria [5]. We performed MRI in all patients to increase the specificity of our diagnosis and the results of our MR imaging were consistent with what has been seen in world literature. MRI confirmed diagnosis of ARVD/C in majority of our patients (80%).

MR imaging allows a three-dimensional evaluation of especially the right ventricle and provides the most important anatomic, functional, and morphologic criteria for diagnosis of ARVD/C within one single study. Although demonstration of morphofunctional abnormalities of the right ventricle, especially fat in the right ventricular myocardium, shows high specificity but low sensitivity, MR imaging appears to be the optimal imaging technique for detection and follow-up of clinically suspected ARVD/C [17]. Addition of fat suppressed T1W sequences has significantly improved interobserver agreement and allowed the reviewers to be more confident in their interpretations. There is a reciprocal relationship between sensitivity and specificity for non fat suppressed and fat suppressed sequences with non fat suppressed sequences showing better sensitivity and fat suppressed sequences showing better specificity [20].

Since the patients with ARVD/C usually have a variable heart rate, fat signal will vary due to varying T1 weighting with increasing RR interval leading to decreased fat signal intensity. Thus factors such as these may result in poor visualization of fat despite being present. Evaluation of wall motion abnormalities in such cases is of immense help in clinching the diagnosis [21]. The sensitivity and specificity of MRI in diagnosis of ARVD/C is 96% and 78% respectively [22].

Limitations of MRI

Unfamiliarity with normal right ventricular morphology and function has led to high interobserver and poor reproducibility in some series [23]. The presence of intramyocardial fat deposition in right ventricle must be interpreted with caution, as fat in right ventricle is present in large proportion of normal individuals (up to 85%) and increases with age, body weight and female gender [24].

We have used comprehensive protocol of T1W non fat sat and T1W fat sat sequences in all our patients along with True free induction in steady state precession (FISP) steady state in free precession (SSFP) for morphology as well as function and post contrast late gadolinium enhancement. We also used right ventricular function evaluation to increase the confidence level of diagnosis.
In conclusion magnetic resonance imaging is a robust and an accurate technique of evaluation of morphological and functional abnormalities in patients with ARVD/C I. The addition of fat suppression sequences improves the interobserver agreement in assessing fibro fatty infiltration of right ventricular wall. Furthermore use of LGE may reveal areas of fibro fatty infiltration hitherto invisible on non contrast sequences.

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Conflict of interest

None.

References


