Arrhythmogenic Right Ventricular Dysplasia: An Under-recognized Form of Inherited Cardiomyopathy

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We report a case of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD) in order to evaluate the course of an under-recognized form of cardiomyopathy with a vast array of clinical manifestations. The patient is a 49-year-old white woman transferred from an outside hospital due to dyspnea and persistent hypoxia. She had a pertinent family history that included a sister who died suddenly in her 30s from unexplained heart failure. Initial work-up for hypoxia was unrevealing. Transthoracic echocardiography revealed isolated right ventricular dysfunction with dilation and multiple trabeculations. Further investigation, including cardiac computed tomography and magnetic resonance imaging, revealed fatty infiltration into the right ventricular wall suggestive of ARVD.

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KEY WORDS

Arrhythmogenic right ventricular dysplasia • Cardiomyopathy • Ventricular arrhythmia • Syncope

Arrhythmogenic right ventricular dysplasia (ARVD) is a rare inherited cardiomyopathy, characterized by progressive replacement of normal heart tissue with fatty or fibrofatty tissue, leading to structural and functional abnormalities, particularly in the right ventricles. Familial pattern of inheritance is observed in approximately 30% to 50% of cases with low penetrance and varying degrees of expression, which makes it difficult to trace and diagnose within members of the family.[1] Symptoms of ARVD are usually secondary ventricular arrhythmias; the most common symptoms are chest palpitations, syncope, and atypical chest pains. The age range of patients diagnosed with ARVD is

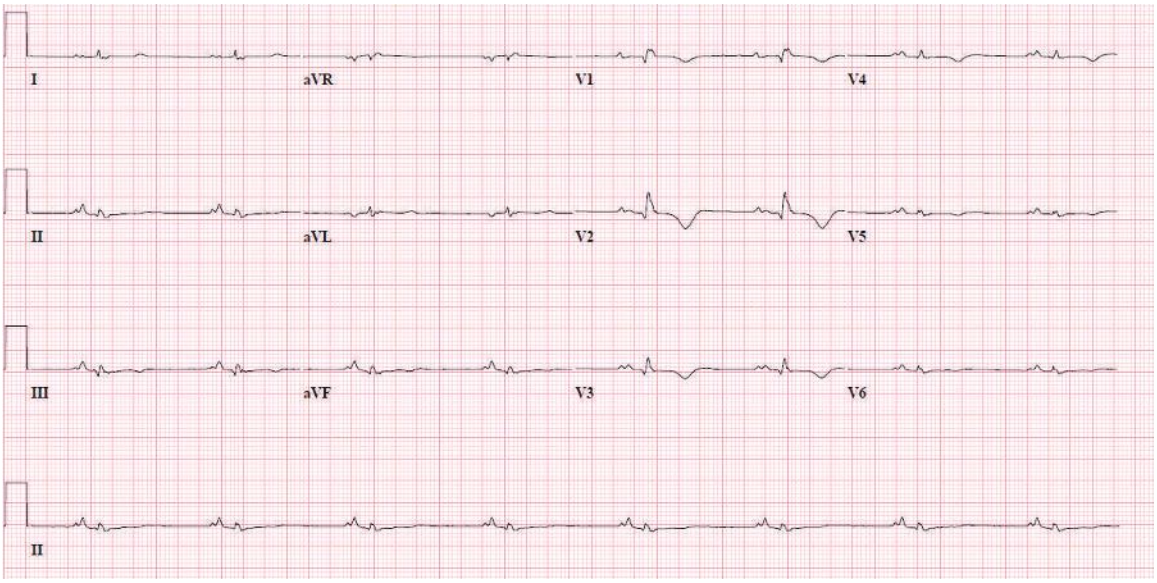


Figure 1. Admission electrocardiogram showing sinus bradycardia with first-degree atrioventricular block (I), incomplete right bundle branch block (II), and biatrial enlargement (III).

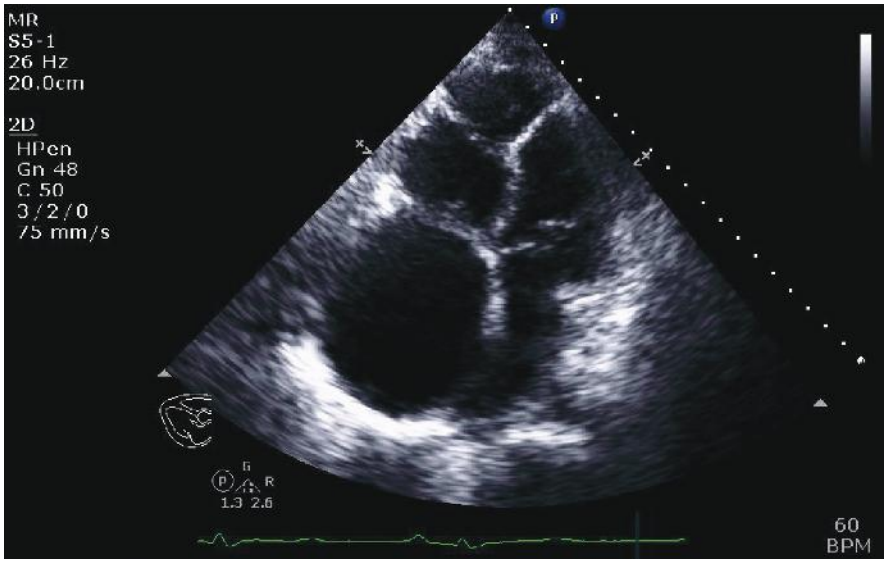
typically between 10 and 50 years.[1,2] Early diagnosis and management is necessary to prevent adverse events such as heart failure and sudden cardiac death.

Presentation

The patient is a 49-year-old white woman who was transferred from an outside hospital due to dyspnea and persistent hypoxia. She has no past cardiac history. However, she revealed that she had a sister who died in her early 30s from unexplained heart failure and "abnormal heart rhythm." She denied any history of smoking, alcohol use, or illicit drug use. The patient noted symptoms of dyspnea that started 2 months prior to presentation. She was seen by her primary care physician and diagnosed with bronchitis. When symptoms failed to improve despite antibiotics and oral steroids, she decided to seek medical attention at her local hospital's emergency room. There she was found to be hypoxic, with an oxygen saturation of 85%. She remained normotensive; however, electrocardiogram (ECG) revealed atrial flutter without rapid ventricular response. She received cardioversion and repeat ECG (Figure 1) revealed sinus bradycardia with intermittent first-degree atrioventricular block and incomplete right bundle branch block. Her hypoxia was further evaluated with chest radiography and ventilation–perfusion scan, results of which were both unrevealing. The patient was then transferred to our institution for a higher level of care.

Upon her arrival she was noted to be in mild respiratory distress and required 3 L of nasal cannula oxygen. However, results of the remainder of her physical examination were unremarkable. Right heart catheterization was significant for high right-sided filling pressures with equalization of right atrial and right ventricular (RV) pressure. Transthoracic echocardiography (Figure 2) revealed severe dilation of the right atrium and isolated RV dysfunction with multiple trabeculations. Transesophageal echocardiography (Figures 3 and 4) revealed severe dilation of the

Figure 2. Transthoracic echocardiogram showing a dilated right atrium (*large arrowhead*) and a dysmorphic right ventricle (*small arrowhead*).



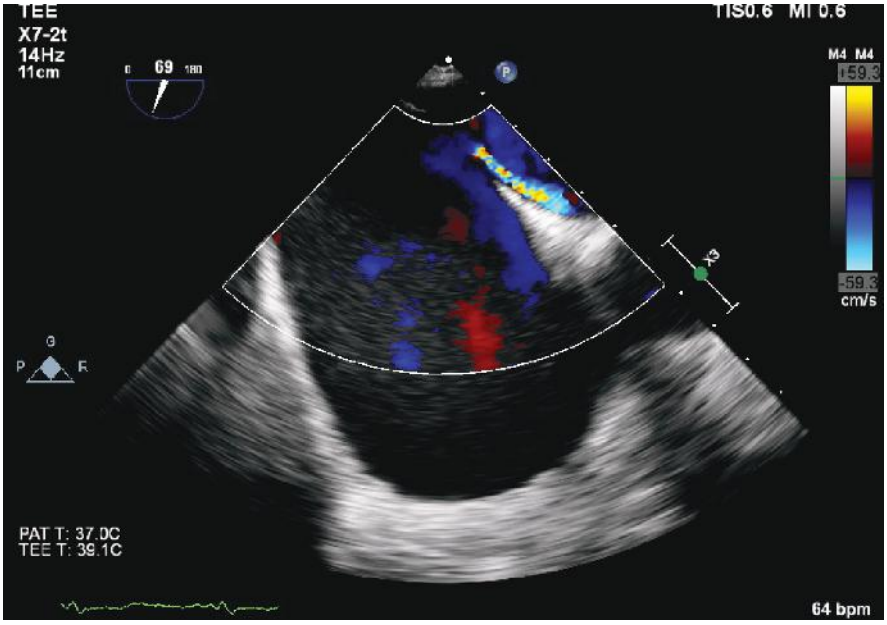


Figure 3. Transesophageal echocardiogram showing a dilated right atrium and patent foramen ovale with continuous shunting.

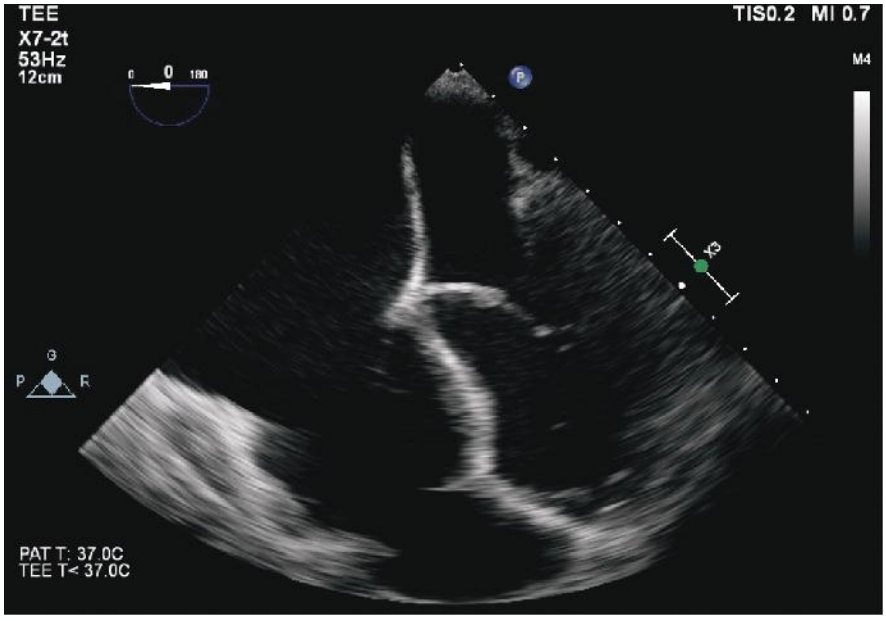
right atrium, small patent foramen ovale with continuous right-to-left shunting, and a dysmorphic right ventricle with severe hypokinesis. Cardiac computed tomography (CT; Figures 5 and 6) was ordered to evaluate for anomalous pulmonary veins, and revealed subtle fat attenuation in the right ventricle; however, motion degradation was noted. Due to our high clinical suspicion, magnetic resonance imaging (MRI; Figure 7) was ordered, which confirmed the diagnosis of ARVD. The patient is currently being evaluated for orthotopic heart transplantation.

Discussion

ARVD is a rare and underrecognized form of inherited cardiomyopathy characterized by ventricular arrhythmias and structural defects of the right ventricle due to an infiltration of fat and/or fibrous tissue in the free wall.[3] Prevalence of ARVD in the general population is estimated to be 1 in 5000.[4] However, due to diverse phenotypic expression, this may be an underestimation. A familial pattern of inheritance of ARVD is observed in 30% to 50% of cases, but is often underestimated due to the underperformance of systematic screening of all family members.[1] There are currently two known patterns of inherited ARVD: autosomal dominant, the most common, and autosomal recessive, associated with Naxos disease. Eight genes are known to be associated with the autosomal dominant form of ARVD, and different mutations show different penetrance, according to recent studies.[1,5] More research is needed to establish the penetrance of different genetic forms of ARVD. This may lead to the inclusion of specific gene mutations in the diagnostic criteria. Our patient had a relevant family history, which could have been contributory to her diagnosis of ARVD. Therefore, it is important to screen family members and perform a complete diagnostic evaluation, if possible. However, familial patterns alone are not sufficient for the diagnosis of this disease.

Symptoms of ARVD can include chest pain, palpitations, and syncope. Although not reported by our patient, syncope is one of the most common presenting symptoms in a patient with ARVD. In a cohort study looking at 163 patients with suspected ARVD, it was reported that approximately two-thirds of the patients had palpitations, one-third had syncopal episodes, and one-quarter had atypical chest pains.[2] Nonsustained or sustained ventricular tachycardia with left bundle branch block is the most common arrhythmia. However, various forms of supraventricular

Figure 4. Transesophageal echocardiogram showing a dilated right atrium (*large arrow*) and a dysmorphic right ventricle (*small arrow*).



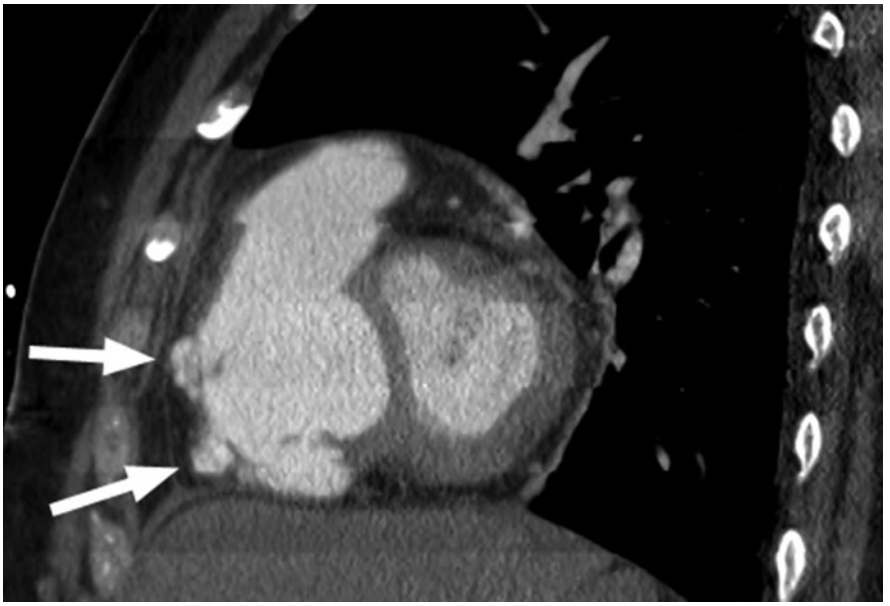


Figure 5. Short-axis reformatted computed tomography image revealing an irregular lobulated right ventricular contour in addition to two aneurysms arising from the right ventricular free wall (*arrows*).

tachycardia, as seen in our patient, have also been reported.[4] The most serious presentation of ARVD is sudden cardiac death (SCD); 20% of patients with ARVD will have SCD as their initial manifestation prior to diagnosis.[4] According to a study analyzing cases of SCD, 14% of 273 SCDs were secondary to ARVD among people aged between 1 and 35 years. The prevalence was up to approximately 30% in young athletes with SCD, making ARVD the second leading cause of death in patients younger than 30 years, after hypertrophic cardiomyopathy. The median age of someone presenting with one of these common symptoms was 29 years and the median age at diagnosis with ARVD while still living was 33.4 years.

Along with its rarity, the nonspecific clinical features of ARVD and familial patterns have facilitated a more multidisciplinary approach in identifying patients with ARVD and gathering information with respect to risk stratification and treatment. The 2010 revision of the Task Force Criteria for ARVD incorporated histologic, structural, arrhythmic, electrocardiographic, and familial features, in order to improve the diagnostic sensitivity and preserve the high diagnostic specificity of the 1994 criteria.[6] Diagnosis of ARVD is made after a thorough examination of the patient's clinical presentation and identification of the major and minor criteria (Table 1).

Electrocardiogram and echocardiogram are noninvasive procedures recommended in all patients with suspected ARVD. During the initial stages of the disease, it may be difficult to make an electrocardiographic diagnosis, as approximately 40% of patients with ARVD have a normal ECG result at presentation.[7] However, throughout the course of the disease, approximately 90% of patients will develop one or more abnormal findings. Approximately 30% of patients with ARVD have classic epsilon waves.[8] This finding is thought to be secondary to the progressive fatty tissue infiltration, which causes prolonged delay of depolarization in the right ventricle, which then causes widening of the QRS complex. Postexcitation waves can occur immediately after the QRS complex, forming an epsilon wave.[8] The presence of epsilon waves may be directly associated with RV dilation. In a previous study, RV dilation was seen in 33% of patients with epsilon waves compared with only 18% of those without epsilon waves.[9] Other right ventricle abnormalities are common, including trabecular derangement, as seen in our patient (Figure 4).[3]

Figure 6. Two-chamber reformatted computed tomography image again shows a markedly enlarged right atrium (*white arrow*) in addition to lobulated right ventricular contour and prominent irregular right ventricular trabeculations (*black arrow*).

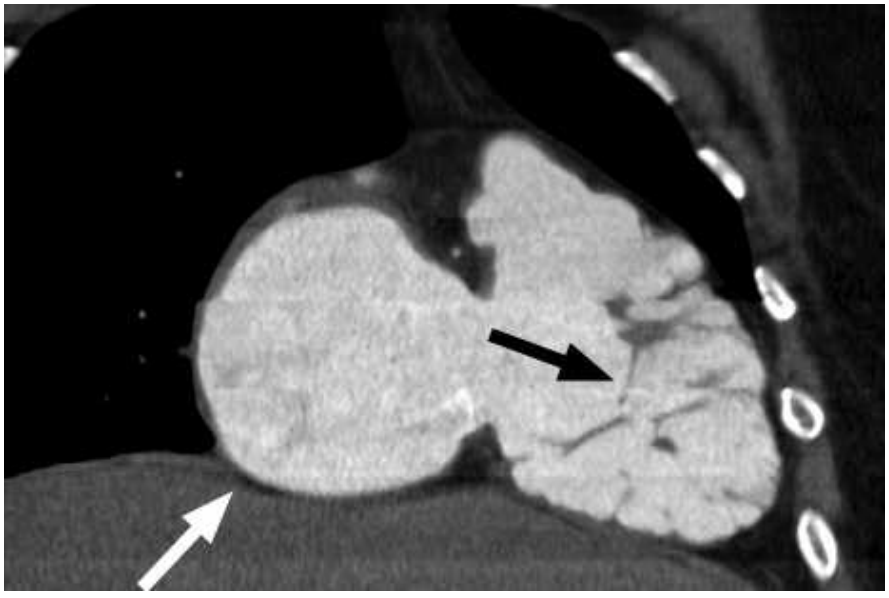


TABLE 1

2010 Revised Task Force Criteria for the Diagnosis of ARVD

	Major Criteria	Minor Criteria
I. Global or regional dysfunction and structural alterations[a]	By 2D echocardiography: • Regional RV akinesia, dyskinesia, or aneurysm • and 1 of the following (end diastole): - PLAX RVOT ≥ 32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) - PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥ 21 mm/m^2) - or fractional area change ≤ 33% By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • and 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m^2 (male) or ≥ 100 mL/m^2 (female) - or RV ejection fraction ≤ 40% By RV angiography: • Regional RV akinesia, dyskinesia, or aneurysm	By 2D echocardiography: • Regional RV akinesia or dyskinesia • and 1 of the following (end diastole): - PLAX RVOT ≥ 29 to < 32 mm (corrected for body size [PLAX/BSA] ≥ 16 to < 19 mm/m^2) - PSAX RVOT ≥ 32 to < 36 mm (corrected for body size [PSAX/BSA] ≥ 18 to < 21 mm/m^2) - or fractional area change > 33% to ≤ 40% By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • and 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥ 100 to < 110 mL/m^2 (in men) or ≥ 90 to < 100 mL/m^2 (in women) - or RV ejection fraction > 40% to ≤ 45%
II. Tissue characterization of wall	• Residual myocytes < 60% by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60%-75% by morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals > 14 y (in the absence of complete RBBB block QRS ≥ 120 ms)	• Inverted T waves in leads V_1 and V_2 in individuals > 14 y (in the absence of complete RBBB) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals > 14 y in the presence of complete RBBB
IV. Depolarization/conduction abnormalities	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	• Late potentials by SAECG in ≥ 1 of the following 3 parameters in the absence of a QRS duration of ≥ 110 ms on the standard ECG - Filtered QRS duration ≥ 114 ms - Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms - Root-mean-square voltage of terminal 40 ms ≤ 20 μV • Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete RBBB
V. Arrhythmias	• Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • > 500 ventricular extrasystoles per 24 h (Holter)
VI. Family history	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation Δ categorized as associated or probably associated with ARVC/D in the patient under evaluation	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (< 35 y) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

Diagnostic terminology for revised criteria:
Definite diagnosis: 2 major, *or* 1 major and 2 minor criteria, *or* 4 minor from different categories.
Borderline diagnosis: 1 major and 1 minor, *or* 3 minor criteria from different categories.
Possible diagnosis: 1 major, *or* 2 minor criteria from different categories.

[a]Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

Δ A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

2D, two-dimensional; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; BSA: body surface area; ECG, electrocardiogram; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RBBB, right bundle branch block; RV, right ventricle; RVOT, RV outflow tract; SAECG, signal-averaged electrocardiography.

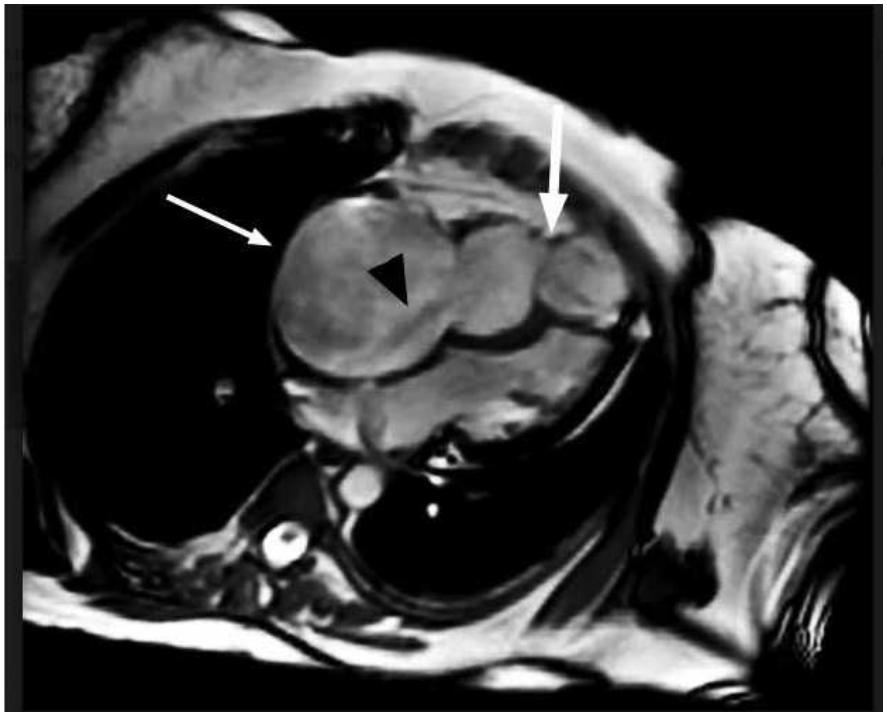


Figure 7. Four-chamber fast imaging employing steady-state acquisition (FIESTA) magnetic resonance image demonstrates an abnormal "waisted" morphology of the right ventricle (*large white arrow*) with irregular trabeculations seen involving the apical portion of the right ventricle. A markedly dilated right atrium is present (*small white arrow*) in addition to a regurgitant jet indicative of tricuspid regurgitation (*black arrowhead*).

MRI is another effective noninvasive imaging technique indicated in the workup of ARVD. It provides a clear visualization of the ventricular wall in addition to providing information regarding functional abnormalities. Pathologic myocardial fatty or fibrofatty infiltration is the cornerstone of ARVD; however, significant myocardial fatty or fibrofatty replacement of the RV wall can be seen in more than 50% of healthy elderly patients.[10] Furthermore, biventricular and isolated left ventricular involvement have also been reported.[4] These findings may lead to difficulties in diagnosis. Although not included in the Task Force criteria, cardiac CT may also play a helpful role in diagnosis, especially in cases in which cardiac MRI may be contraindicated.

Primary and secondary prevention of SCD with an implantable cardioverter-defibrillator (ICD) remains the primary cornerstone of treatment. Previous studies evaluating efficacy of ICD prevention of SCD in patients with ARVD have shown favorable results. One multicenter study of 132 patients showed that 48% of patients with ARVD had appropriate ICD interventions, with a 96% survival rate at 36-month follow-up.[11] For patients who are not good candidates for implantation, antiarrhythmic drug therapy might aid to minimize symptomatic arrhythmia.[4] To our knowledge, there is very little evidence comparing ICD versus antiarrhythmic therapy. Therefore, guidelines for management of these patients remain elusive. Precursors of SCD still have not been clearly delineated, which makes

MAIN POINTS

- Arrhythmogenic right ventricular dysplasia (ARVD) is a rare inherited cardiomyopathy, characterized by progressive replacement of normal heart tissue with fatty or fibrofatty tissue, leading to structural and functional abnormalities, particularly in the right ventricles.
- There are currently two known patterns of inherited ARVD: autosomal dominant, the most common, and autosomal recessive, associated with Naxos disease. Eight genes are known to be associated with the autosomal dominant form of ARVD.
- Electrocardiogram and echocardiogram are noninvasive procedures recommended in all patients with suspected ARVD. Magnetic resonance imaging is another effective noninvasive imaging technique indicated in the workup of ARVD. It provides a clear visualization of the ventricular wall in addition to providing information regarding functional abnormalities.
- Primary and secondary prevention of sudden cardiac death (SCD) with an implantable cardioverter-defibrillator (ICD) remains the primary cornerstone of treatment. Previous studies evaluating efficacy of ICD prevention of SCD in patients with ARVD have shown favorable results.

management of asymptomatic patients unclear, especially in patients who show only mild morphologic abnormalities. However, all patients with confirmed ARVD should be counseled to avoid any strenuous activity. ■

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