ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA - CASE REPORT FROM PAKISTAN AND REVIEW OF LITERATURE

AAMIR HAMEED, MBBS, FCPS[1], NASIR REHMAN, MBBS[2] AND FAHIM H. JAFARY, M.D[3]

INTRODUCTION

Arrhythmogenic right ventricular dysplasia (ARVD) is disorder of cardiac muscle characterized by the replacement of myocytes by fibrofatty tissue and extracellular matrix (1). It is a relatively rare disease and the prevalence is estimated to be 1:5000 in the west (2). Although described in 1977, the first report in the English literature came from Marcus and colleagues (3) who described a series of 24 cases in 1982. The presentation varies from an asymptomatic state to heart failure, symptomatic ventricular tachycardia (VT) and sudden cardiac death (SCD). There are no data on the prevalence of ARVD in the Pakistani (or South Asian) population. There are no data on the Pakistani population. However, one may suspect that this disease is probably far more common than what may be conventionally thought, particularly since consanguineous marriages are very common in Pakistan. This would lend to propagation of the genetic factors that lead to ARVD. The literature on South Asians is limited to case reports (4,5). We describe a case of ARVD who presented with SCD to a tertiary care hospital in Pakistan. We then review the pathogenetic mechanisms, diagnostic criteria as well as therapeutic options and highlight the difficulties in managing patients in this part of the world, given the stringent financial constrains.

Case Report

A 55-year-old retired soldier from Gilgit in northern Pakistan was referred to our hospital with a three-year history of intermittent retrosternal chest discomfort and a few months history of progressively increasing dyspnea. At presentation, he was limited to walking a few steps. A few weeks prior to presentation he suffered a syncopal episode and presented to a local hospital. At that time he was found to be in sustained ventricular tachycardia, requiring cardioversion and treatment with antiarrhythmic drugs. However, no specific etiology of this patient's arrhythmia was identified. At presentation to our hospital, the patient had overt signs of right heart failure. The ECG showed an incomplete RBBB with nonspecifc T wave changes in the anterior leads. An echocardiogram showed normal left ventricular function, a massively dilated and poorly contracting right ventricle. In addition, there was hypertrophy of the moderator band and akinesis and loss of muscle at the right ventricular apex. A coronary angiogram was negative for any obstructive disease. Angiography of the right ventricle revealed massive dilatation, trabecular thickening and localized bulging. A tentative diagnosis of ARVD was made in view of the clinical and echocardiographic features. The patient improved somewhat with diuretics. Cost constrains did not permit the implantation of an implantable defibrillator and the patient was discharged on oral amiodarone.

Discussion

ARVD is a genetic cardiomyopathy characterized by fibrous-adipose substitution of the right (6) and rarely of the left ventricular myocardium (7). The term "arrhythmogenic" alludes to the propensity of patients with this disorder to develop ventricular arrhythmias which are frequently sustained and associated with SCD 8. The disease tends to run in families in 50% of the cases with autosomal dominant inheritance (9). However, a recessive mode of inheritance is also known to occur. The dominant forms have been mapped to loci at chromosomes 14, 1, 2, 3 and 10 (10). While the exact molecular mechanisms that lead to myocardial replacement with fibrous tissue remain ill defined, it is speculated that a

1 Senior Instructor, Section of Cardiology
2 Senior Resident, Department of Medicine
3 Assistant Professor & Consultant Cardiologist, Section of Cardiology, Aga Khan University Hospital, Karachi, Pakistan

combination of apoptosis, inflammation and muscle dystrophy play an operative role (11).

Clinical Presentation: The clinical presentation of ARVD is varied. It frequently is asymptomatic until the adolescent age. The key to making the diagnosis is suspecting the presence of ARVD, particularly in any young patient presenting with a ventricular arrhythmia, syncope, sudden cardiac death (SCD), heart failure or in a patient with a family history of SCD.

1. **Sudden Cardiac Death:** The most devastating presentation of ARVD is SCD, which may occur as the initial presentation of this disease. This tends to more frequent in young athletes (12,13). It is estimated to be the culprit in approximately 3-4% of athlete sudden deaths (14). In some parts of Italy this number is much higher - approximately 20% 8. The mechanism is thought to be catecholamine induced ventricular tachycardia, which degenerates into fibrillation.

2. **Ventricular arrhythmias:** Ventricular arrhythmias can range from asymptomatic ventricular premature beats to sustained lethal tachycardias leading to SCD. Typically, the ventricular tachycardia originates from the right ventricle and, therefore, is of left bundle branch (LBB) morphology. These ventricular arrhythmias tend to be provoked by catecholamines, as evident by a high rate of inducibility with isoprenaline infusion (15) as well as the preponderance of sudden death with exertion in this population.

3. **Heart Failure:** Heart failure in ARVD sets in as the disease progresses and cardiac function declines. Heart failure is predominantly of the right heart type, although in a distinct subset, biventricular failure is seen as a result of concomitant left ventricular involvement 7,16. In these patients, the differentiation between ARVD and idiopathic dilated cardiomyopathy is often difficult. This distinction is of more than academic significance as the propensity to lethal arrhythmias in ARVD would prompt more aggressive therapy designed to prevent SCD. It has been suggested that the diagnosis of ARVD should be suspected in patients with dilated cardiomyopathies who have anterior precordial T wave abnormalities. Usually heart failure is seen late in the course of the disease and portends a very adverse prognosis.

Diagnosis: The diagnosis of ARVD is difficult as the clinical and laboratory features are subtle and frequently missed. No single feature is diagnostic. Central to making the correct diagnosis is suspecting the diagnosis. Several diagnostic modalities are available.

1. **Endomyocardial Biopsy:** The only definite method of diagnosis is histological, either at necropsy or via endomyocardial biopsy. The latter is difficult because the disease is frequently patchy, leading to the possibility of missing the disease. Moreover, the common site of biopsy, the interventricular septum, is often spared in ARVD 1. Thus, endomyocardial biopsy is rarely used to make the diagnosis in the present day and age. Moreover, in Pakistan, although cardiologists trained to perform the procedure are available (including one of the authors), the local experience in reading cardiac biopsies is fairly limited.

2. **Electrocardiography** (ECG) is a routine test performed in most patients suffering from heart disease. The ECG is frequently nonspecific; the most common abnormalities seen are T wave inversions in the right precordial leads with or without some sort of right ventricular conduction delay (complete or incomplete right bundle branch block). However, the most specific ECG abnormality is the post excitation "epsilon" wave that is a small amplitude after potential that occurs at the end of the QRS complex 17 (figure). This is seen in approximately 30 % of patients with ARVD 18.

3. **Echocardiography:** Following the ECG, echocardiography is frequently the first non-invasive that is performed in patients with suspected ARVD. Table 1 shows the pathognomonic echocardiographic features of ARVD. The reported sensitivity and specificity of echocardiography for detecting ARVD is 86% and 93% respectively. It is also useful to exclude other conditions like Ebstein's anomaly which

Table-I

Echocardiographic Features of ARVD
* RV dilatation
* Segmental RV dilatation with or without dyskinetic Segments (aneurysms or bulgings)
* Bulging of the RV during diastole
* Dyskinesia of the inferobasal free wall during systole
* Dyskinesia of the apex
* Exaggerated trabecular pattern in the RV
* Structural abnormalities of the moderator band including hypertrophy and increased reflectivity

mimic ARVD (19). It is of vital importance to note that the diagnosis of ARVD is frequently missed on a routine echocardiogram unless these features are specifically looked for. Moreover, at times only subtle features are present, like hypertrophy or increased reflectivity of the moderator band and prominent trabeculations of the right ventricular apex. Thus, when the diagnosis is suspected the echocardiographer and the interpreting physician should be made aware of the suspicion prior to the test.

4. **Right ventricular contrast angiography** remains the gold standard for making the diagnosis, although echocardiography and nuclear magnetic resonance imaging (MRI) have more or less superceded this technique. Views are taken in the 45° RAO angulation. Characteristic angiographic features include localized morphologic and contraction abnormalities in the right ventricular free wall in the form of akinesis or dyskinesis with localized bulgings. These bulgings tend to be more common at the infundibular, apical and right ventricular outflow tract, forming the so-called "triangle of dysplasia and have a diagnostic specificity of over 90% (20). Other features frequently seen include trabecular thickening leading to an impression of "deep fissures" and a prominent moderator band.

5. **MRI** uniquely allows distinction between fibrofatty tissue and myocardium (21) and is emerging as a very useful tool for the diagnosis of ARVD. MRI features considered strongly supportive of the diagnosis include high-intensity areas indicating fatty substitution of myocardium along with bulgings of the right ventricular outflow tract and dilation of the right ventricle (22). The addition of motion detection to MRI (cine-MRI) allows the evaluation of right ventricular function in addition to structure. However, formal validation of these echocardiographic criteria remains to be performed. Further, cardiac MRI, in particular cine-MRI has limited availability, even in the west. Nevertheless, MR imaging appears to be the optimal technique for the detection and follow-up of clinically suspected ARVD 2.

In view of the heterogeneity of presentation, a consensus group proposed a set of major and minor criteria to facilitate the diagnosis of ARVD 1. The diagnosis of ARVD requires the presence of either two major or one major + two minor, or four minor criteria (table 2).

Evaluation and Treatment: An important focus of the evaluation of a patient diagnosed with ARVD is to identify those at risk for SCD. The risk of SCD is approximately 3% per year 2 and in some patients can be the initial manifestation of ARVD. Thus the cumulative risk for an individual patient is substantial. Retrospective analyses suggests that extensive right ventricular dysfunction, left ventricular involvement, syncope, a family history of SCD, strenuous sport activities and a history of ventricular tachycardia are risk factors for SCD in an individual patient. Unfortunately there are no prospective studies that have evaluated the predictive value of these risk factors. Moreover, the efficacy of a variety of strategies in preventing SCD in these patients is unclear. In addition, the risk of SCD is progressive with time and therefore, for an individual patient, the decision to withhold therapy (be it pharmacological or non-pharmacological) to prevent SCD on the basis of a presumed "low risk" profile is, intuitively, difficult. All patients should undergo a 24-hour holter monitoring study as well as an exercise tolerance test. Further testing and therapy is dictated by the patient's clinical profile. Patients presenting with either high-risk characteristics for SCD or sustained ventricular arrhythmias should be considered for electrophysiological (EP) testing to determine the nature of the arrhythmia as well as the best therapeutic option. EP testing is now available in Pakistan at several tertiary centers.

Table-II

Criteria for the Diagnosis of RV Dysplasia, *(From: Reference 1)*

I.	**Family History**
	Major
	Familial disease confirmed at surgery or necropsy
	Minor
	Family history of premature sudden death (>35) caused by suspected ARVD
	Family history (clinical diagnosis based on present criteria)
II.	**ECG depolarization/conduction abnormalities**
	Major
	Epsilon waves or localized prolongation (>110ms) of the QRS complex in the right prescordial leads (V1 - V3)
III.	**ECG repolarization abnormalities**
	Minor
	Inverted T wave changes in teh right precordial leads (V2 and V3) in people > 12 years and in the absence of right bundle branch block
IV.	**Arrhythmias**
	Minor
	Sustained and non-sustained left bundle branch block type ventricular tachycardia documented on the ECG, Holter monitoring or during stress testing. Frequent ventricular extrasystoles (>1000/24hrs on Holter monitoring)
V.	**Global and regional dysfunction and structural alterations**
	Major
	Severe dilatation and reduction of the right ventricular ejection fraction with no (or only mild) left ventricular involvement.
	Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulgings)
	Severe segmental dilatation of the right ventricle
	Minor
	Mild global right ventricular dilatation of the right ventricle
	Regional right ventricular hypokinesia
VI.	**Tissue characteristics of walls**
	Major
	Fibrofatty replacement of myocardium on endomyocardial biopsy

1. **Drug Therapy:** In asymptomatic patients or those with non-lethal arrhythmias, beta-blockers are a reasonable starting point. Sotalol has been reported to be the most effective drug in suppressing ventricular arrhythmias in patients with ARVD (23). Amiodarone is also effective in this setting 18. Drug therapy may be continued as an adjunct to an implantable cardioverter-defibrillator (ICD) (see below) or as primary therapy for sustained arrhythmias. In the latter, therapy can be guided by repeated EP testing. Patients with ARVD who have survived a lethal ventricular arrhythmia or SCD should be prohibited from competitive sports as ventricular fibrillation may recur despite drug or non-pharmacological therapy.

2. **Radiofrequency Ablation:** Radiofrequency ablation (RFA) of an active focus is an alternative therapy that can be used in patients not responding to drug therapy. Another group of patients where the procedure is indicated are those who have received an ICD but suffer from recurrent ventricular arrhythmias (leading to ICD discharges). Success rates are variable and recurrences are frequent, often due to a new focus 24 taking over.

3. **ICD Implantation:** Patients presenting with either hemodynamically unstable ventricular tachycardia or SCD should be considered for ICD implantation. Unfortunately, in Pakistan, cost constrains render this option virtually impossible for most patients. Nevertheless, the procedure is available at several centers in Pakistan. It is thought that the ICD confers a long-term benefit on prognosis in ARVD although this has not been unequivocally established. Further, the procedure of implantation is much more complicated in patients with ARVD due to the thinning of the

right ventricular wall and patchy fibrosis. Thus only trained and experienced operators should be doing this procedure.

4. **Surgery:** Usually the last resort, surgical resection of a ventricular focus has been performed in patients with resistant ventricular arrhythmias with variable success. Ultimately, heart transplantation is a surgical option that is considered in patients who are severely dyspneic.

Conclusion: ARVD is a rare disorder with a very heterogenous presentation. The disease is frequently asymptomatic until adolescence and the findings on testing are subtle - hence frequently missed. It is usually progressive. Suspecting ARVD is key to making the diagnosis. The disease should be suspected in any patient with unexplained right heart failure or ventricular arrhythmias / SCD particularly when the heart on routine examination appears to be normal. Evaluation needs to focus on identifying those at risk for SCD while therapy is geared towards preventing this devastating complication. The true prevalence of ARVD in Pakistan is unknown but, given the highly common practice of consanguineous marriages, one may speculate that ARVD may not be uncommon in our population. Thus, physicians should be on the lookout for this condition

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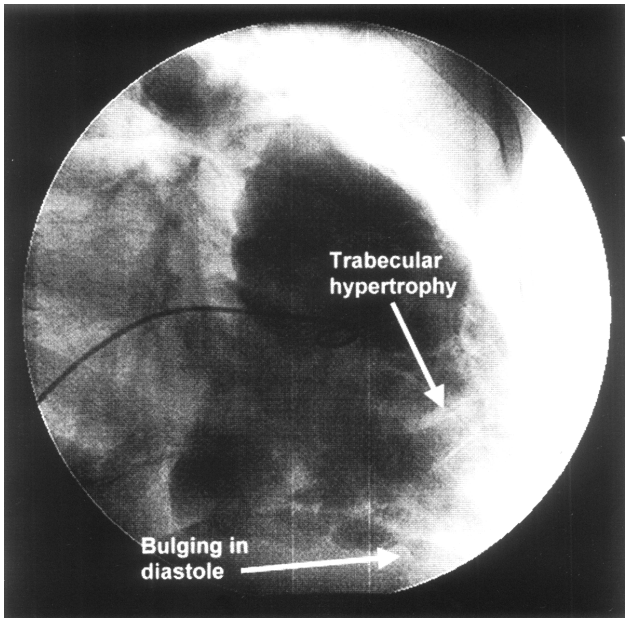

Figure-I
Right ventricular angiogram revealing massive dilatation of the RV, thickening of trabeculae rendering an appearance of "fissures" and localized bulgings in diastole.

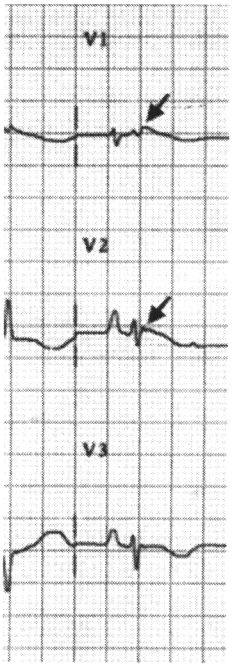

Figure-II
Precordial leads in ARVD. Arrows point to "epsilon" wave, small amplitude after potentials that are pathognomonic for this condition.