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CLINICAL PROFILE OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Lubna Noor[1], Yasir Adnan[2], Mohammad Faheem[3], Shahab Ud Din[4], Amina[5], Kamran Bangash[6], Zahid Aslam Awan[7]

[1,2] Department of Cardiology, Lady Reading Hospital, PGMI, Peshawar, Pakistan
[3,5] Department of Cardiology, Khyber Teaching Hospital, Peshawar, Pakistan
[4,6,7] Department of Cardiology, Hayatabad Medical Complex, Peshawar, Pakistan

Address for Correspondence:

Dr. Lubna Noor,

Department of Cardiology, Lady Reading Hospital, PGMI, Peshawar, Pakistan

E-mail: lubnanur@yahoo.com

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ABSTRACT

Objective: To study the clinical profile of patients with ARVC in the province of Khyber Pakhtunkhwa (KP).

Methodology: This prospective observational study was carried out at the department of Cardiology in Hayatabad Medical Complex, PGMI, Peshawar from April, 2008 to March, 2011. The Task Force Criteria 2004 was employed to diagnose the patients. Clinical data of the patients including age, gender, family history, presenting symptoms, twelve lead resting ECG, 24-hours ECG Holter monitoring, signal-average ECG, 2-dimensional transthoracic echo and right ventriculograms were analyzed.

Results: Twenty-eight patients, fulfilling the diagnostic criteria, were included. The mean age at clinical presentation was 30.22±11.88 (range 18 to 42 years), with a male: female ratio of 3.66:1. Twenty-six (92%) presented with VT of LBBB morphology, all patients (100%) had history of palpitations, and 7 patients (25%) had positive family members as well. Various ECG findings were found in 42 to 96% of the patients, SAECG showed late potentials in 12% of the patients, and Holter monitoring yielded various findings in 67 to 92% of the patients. Among imaging modalities, 2-D echo picked up positive findings in 3.5 to 85% of the patients, while RV-gram was helpful in 25 to 46% of the patients.

Conclusion: ARVC mostly presents either with palpitations or VT of LBBB morphology. 12 lead resting ECG and 2-D transthoracic echo are mostly helpful in the diagnosis.

Key Words: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Sudden Cardiac Death (SCD), Ventricular Tachycardia (VT), Left Bundle Branch Block (LBBB)

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic form of cardiomyopathy that primarily affects the right ventricle (RV), culminating in life-threatening ventricular arrhythmias, prompting sudden cardiac death (SCD) and/or eventually right heart failure leading to biventricular heart failure.[1–3] ARVC/D is uncommon but may account for up to 20% of cases of sudden death among young individuals.[3]

ARVC/D was first described by the Pope's physician, Giovanni Maria Lancisi, in his book entitled De Motu Cordis et Aneurysmatibus, published in 1736.[4] The first comprehensive clinical description of the disease was reported by Marcus et al in 1982, when he reported 24 adult cases with ventricular tachyarrhythmias with left bundle branch morphology.[5] Nevertheless, it was not until 1984 that the electrocardiographic features of the disease were first described, including the epsilon wave.[6] Echocardiographic features of thinning of the wall with chamber dilation and aneurysm formation were later elaborated.[7] Recognition of the problems in diagnosing ARVC/D and the fact that there is no "gold standard" or single test that is diagnostic of ARVC/D led to the formation of a task force that put forth major and minor criteria in 1994 to aid in the diagnosis.[8]

ARVC/D has evolved from initially being considered a primary electrophysiological disorder in the late 1980s-1990s to a diagnostic imaging challenge in the 2000s (specifically by MRI) and more recently better understood as a progressive cardiomyopathy explained by a defect in a variety of cell adhesion proteins or intracellular signaling components. The clinical manifestations of ARVC also vary greatly, especially in different ethnic groups.[9] This is probably secondary to its genetic heterogeneity and variable phenotypic expression, along with a diverse disease progression, which make its diagnosis difficult.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), reportedly a rare disorder, has been relatively frequently diagnosed in our set up. It is a disorder that involves replacement of the right ventricular myocardium with fibro-fatty tissue. The present study presents a cohort of ARVC patients who presented to Hayatabad Medical Complex, Peshawar with different clinical manifestations and eventually diagnosed as ARVC.

METHODOLOGY

This prospective observational study was carried out at the department of Cardiology in Hayatabad Medical Complex, PGMI, Peshawar from April, 2008 to March, 2011. All consecutive patients presenting through OPD, ER or private clinics were included. The Task Force Criteria 1994 was employed to diagnose the patients Table 1.[8]

Most of the patients presented with sustained VT with LBBB morphology. Following termination of the VT, either by DC-shock or by IV medications (amiodarone), investigation of the underlying cause of the VT showed that it was due to ARVC. The diagnosis was initially suspected when the resting ECG during sinus rhythm showed T wave inversion in the anterior precordial leads, complete or incomplete RBBB, and/or epsilon wave. Transthoracic 2-D echocardiography, Signal averaged ECG (SAECG) and 24 hours Holter monitoring was done in all patients. Coronary angiography was done in patients who were 40 years old or above. A right ventriculogram was also done but only for 13 patients while others did not consent for the invasive test. Magnetic resonance imaging was not available. Myocardial biopsies were not done in any patient. Standard protocols for the 12 lead ECG, SAECG, Holter monitoring, echocardiogram and

Table 1: Task Force Criteria for Diagnosis of ARVC

2 Major Criteria or 1 Major Plus 2 Minor Criteria or 4 Minor Criteria

	Major Criteria	Minor Criteria
Family History	Familial disease confirmed at necroscopy or surgery	Familial history of premature sudden death (35 years of age) due to suspected ARVD. Family history (Clinical diagnosis based on present criteria)
ECG Abnormalities	Epsilon waves or localized prolongation (<110ns) of QRS complex in right precordial leads (V1-V3)	Late potential on signal averaged ECG. Inverted T Waves in right precordial leads (V2-V3) in subjects > 12 years of age and in the absence or right bundle branch block
Arrhythmias	Sustained or nonsustained LBBB-like ventricular tachycardia documented on ECG or Holter monitoring or during exercise testing. Freqent ventricular extrasystoles (1000/24 h) on Holter	
Structural Abnormalities and Global or Regional dysfunction*	Severe dilatation and reduction of RV ejection fraction with no or mild LV involvement. Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulgings). Severe segmental dilatation of RV.	Mild global RV dilatation or ejection fraction reduction with normal LV. Mild segmental dilatation of RV. Regional RV hypokinesia
Tissue Characteristics of walls	Fibro-fatty replacement of myocardium on endomyocardial biopsy	

ARVD indicates arrhythmogenic right ventricular dysplasia;
LBBB, left bundle branch block;
LV, left ventricle; RV, right ventricle

*Detected by Echo, Angiography, MRI, Radionuclide scintigraphy

right ventriculogram were adapted from the website www.arvd.org.[10]

Twenty-eight patients fully met the diagnostic Task Force criteria. The study was approved by the local ethical committee and all patients gave their informed consent.

RESULTS

Twenty-eight patients (21 males) were diagnosed with ARVC. Mean age at clinical presentation was 30.22±11.88 (range 18 to 42) years. Seven patients (25%) had positive family history of ARVC or premature sudden cardiac death. The commonest presenting symptoms were palpitation (73%) and dizziness (46%). Spontaneous ventricular tachycardia (Figure 1) was the presenting arrhythmia in 26 patients (92%) and 1 (3.5%) with ventricular fibrillation and cardiac arrest.

According to Table 2, 42 to 96% of the patients had various minor and major ECG abnormalities (Epsilon wave in Figure 2) as defined by the Task Force. SAECG showed late potentials in 12% of the patients (Figure 3), and Holter monitoring yielded various findings in 67 to 92% of the patients (Figure 4). Echocardiography supported the Task Force Criteria in 3.5 to 85% as far as right ventricular involvement was concerned (Figure 5), while only one patient had mild left ventricular systolic dysfunction. Only 13 patients (46%) of the patients consented for angiogram. All of them had normal coronary arteries and left ventriculogram but right ventricular involvement was seen in all, as shown in Table 2.

DISCUSSION

The diagnosis of ARVC/D relies on the demonstration of structural, functional, and electrophysiological abnormalities that are caused by or reflect the underlying histological changes. Technical advances in various imaging modalities have improved the capability to image the RV with reproducible results.[11] There also have been recent developments to assess RV wall thinning and wall motion abnormalities and fatty infiltration of the myocardium by

Figure 1: Ventricular Tachycardia of LBBB Morphology

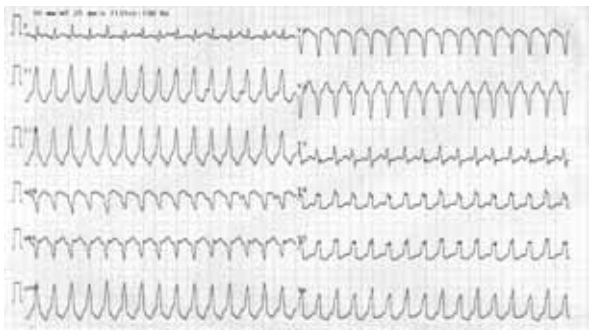


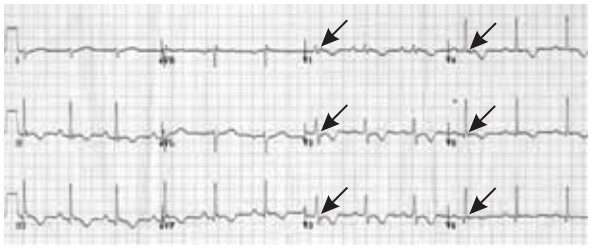
Table 2: Findings of Various Investigation Modalities in Support of Task Force Criteria 1994 for the Diagnosis of ARVC

Investig-ations	Findings	No. of Patients n = 28 (%)
ECG	T wave inversions beyond V1 to V3	27(96)
	QRS prolongation ⩾ 110ms	19(67)
	RBBB	14(50)
	Epsilon waves	12(42)
SAECG	Late potentials positive	12 (42)
HOLTER MONITORING	⩾ 1000 PVC's in 24 hours	26(92)
	Ventricular couplets	19(67)
	Ventricular triplets	19(67)
	Non-sustained VT	21(75)
	VF	None
ECHO	Global RV dilatation	18(64)
	Regional RV hypokinesia	20(71)
	RV apical dilatation	24(85)
	Localized apical aneurysm	02(07)
	No/mild LV involvement	01(3.5)
RIGHT VENTRIC-ULOGRAM	Global RV dilatation	10(35)
	Regional RV hypokinesia	13(46)
	RV apical dilatation	13(46)
	Localized apical aneurysm	07(25)

MRI.[12] Also, it is now possible to quantitate the extent of right ventricular wall motion abnormalities by angiography using computer based analysis as well as to determine right ventricular volumes and ejection fraction.[13]

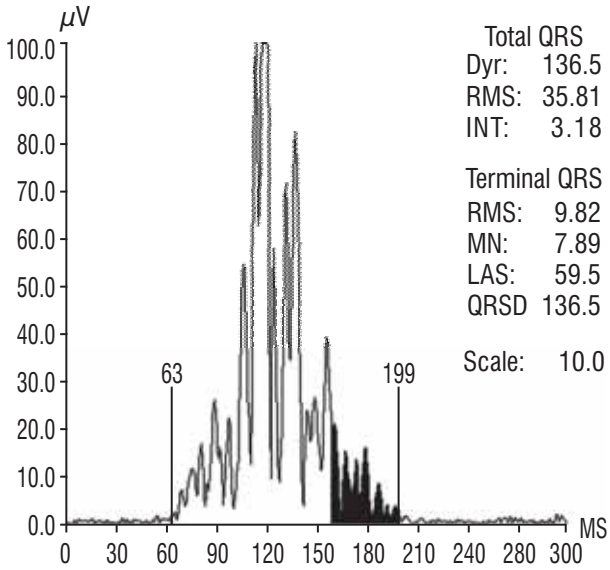
Standardized protocols for performance of these diagnostic studies (ECG, SAECG, echocardiogram, right ventricular angiogram and MRI) are available on www.arvd.org. Repolarization abnormalities are early and sensitive markers of disease expression in ARVC. T-wave inversion in V1, V2

Figure 2: Resting ECG Showing Epsilon Wave (Arrow Heads)



and V3 and beyond in individuals over the age of 14 who are otherwise healthy has been reported in only 4% of healthy women and 1% of men in this age group. Therefore it is reasonably specific in this population and considered a major diagnostic abnormality in ARVC. Depolarization delay in right precordial leads is also common in ARVC. Evaluation of the duration of terminal QRS activation incorporates slurring of the S wave, as well as R prime, into a single measure of terminal activation duration (TAD).[14] Depolarization abnormalities cannot be evaluated in the presence of typical complete RBBB with terminal delay in leads I and V6. However, T wave inversion in V1, V2, V3 and V4 is uncommon in patients with RBBB who do not have ARVC and are frequently seen in those who do have the disease. An abnormal signal averaged electrocardiogram (SAECG) is based on time domain criteria with cutoffs generated from ROC curves.[15,16] The presence of LBBB VT with an inferior axis (R wave positive in II and III, and negative in AVL) is typical of focal RVOT tachycardia.[17] Similar features may be seen in patients with ARVC, but usually coexist with anterior T wave inversion and ventricular

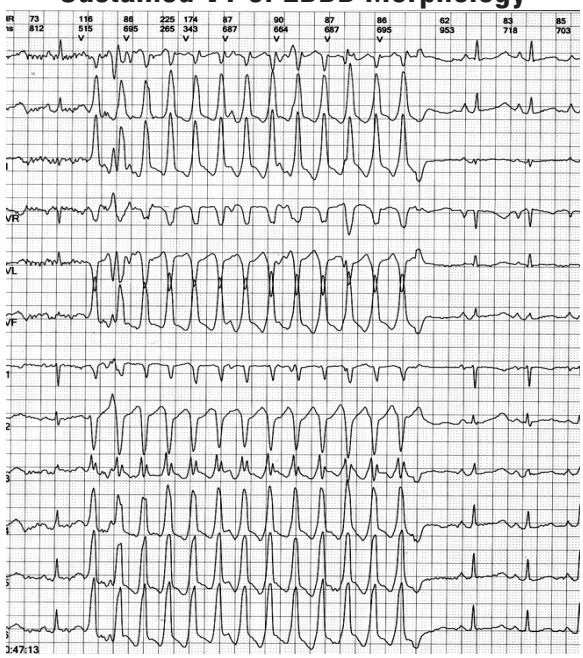
Figure 3: SAECG Showing Positive Late Potentials



arrhythmias of LBBB morphology. The presence of ventricular ectopy increases with age but >200 ventricular premature beats in 24 hours in an adult below age 50 suggests underlying myocardial disease.[18] Additionally, the new ECG criteria have been applied to known ARVC cohorts and have shown an increase in diagnostic value.[19]

In North-American Multidisciplinary Study, various analyses were performed to evaluate how the models with fewer than the full set of investigations would perform in diagnosing affected ARVC patients. The best performance was achieved when a five-variable model was considered, consisting of echocardiogram, RV angiogram, ECG, SAECG, and Holter,

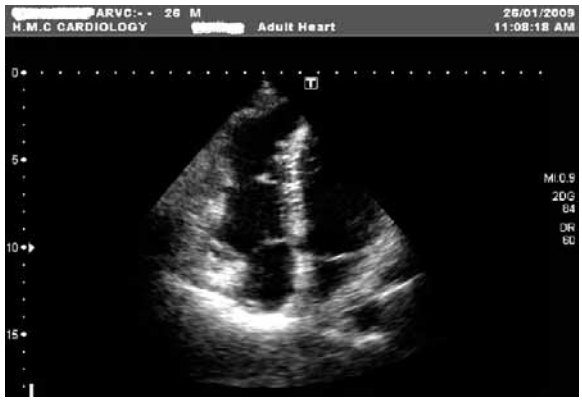
Figure 4: Holter Monitoring Showing Non-Sustained VT of LBBB Morphology



and MRI and RV biopsy were removed. This model was only marginally inferior to the six- and seven-variable model. When four- and three variable models were used, the diagnostic performance of testing was significantly compromised. Based on the analyses of the models, the authors concluded that evaluating RV echocardiogram, RV angiogram, and SAECG is optimal for all successful models. Routinely used ECG and Holter tests complement these tests, providing best diagnostic performance.[20]

Awareness is growing that ARVC is the well-recognized form of a broad disease spectrum that includes left dominant and biventricular subtypes. Lack of specific diagnostic guidelines contributes to under recognition of non-classic disease. Further revisions and modification of the original Task Force Criteria has filled this gap by incorporating

Figure 5: 2-D Transthoracic Echo Showing Regional RV Dilatations



features such as ventricular tachycardia of right bundle branch morphology, subepicardial or midmyocardial late enhancement on magnetic resonance imaging, and global or regional left ventricular dysfunction in patients presenting with arrhythmia rather than heart failure.[8,9] With the identification of disease causing genes, there is the potential for diagnostic mutation analysis and improved pedigree evaluation with better understanding of the natural history, pathogenesis and development of targeted therapies. Individuals who carry newly discovered disease causing genes, but who have incomplete or no disease expression will be recognized; their natural history and appropriate management remains to be determined.

ARVC is a progressive disease with life-threatening complications, which constitute a clinical diagnostic challenge for physicians, given the different genotypic and phenotypic variations and the wide ranges of clinical manifestations. The main challenge is to improve the risk stratification for better identification of high risk patients of SCD and heart failure, who most benefit from early intervention with lifestyle changes, restriction of physical activity, antiarrhythmic drugs, ICD placement, new ablation approaches with simultaneous endocardial and epicardial ablation and, if necessary, heart transplantation. These interventions are available and lifesaving, with the potential to change the natural history of the disease by offering a good quality and better life expectancy.

CONCLUSION

ARVC mostly presents either with palpitations or VT of LBBB morphology. 12 lead resting ECG and 2-D transthoracic echo are mostly helpful in the diagnosis.

REFERENCES

1. Kies P, Bootsma M, Bax J, Schalij MJ, van der Wall EE. Arrhythmogenic right ventricular dysplasia / cardiomyopathy: screening, diagnosis, and treatment. Heart Rhythm 2006;3:225-34.
2. Fontaine G, Frank R, Fontaliran F, Lascault G, Tonet J. Right ventricular tachycardias. In: Parmley WW, Chatterjee K, editors. Cardiology. New York, NY: JB Lippincott Co;1992. p. 1-17.
3. Marcus FI. Right ventricular dysplasia: evaluation and management in relation to sports activities. In: Estes NAM, Salem DN, Wang PJ, editors. Sudden cardiac death in the athlete. Armonk, NY: Futura Publishing Co., 1998. p. 277-84.
4. Lancisi GM. De Motu Cordis et Aneurysmatibus Opus Posthumum In Duas Partes Divisum. Rome: Giovanni Maria Salvioni; 1728.
5. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384-98.
6. Fontaine G, Frank R, Guiraudon G, Pavie A, Tereau Y, Chomette G, et al. Significance of intraventricular conduction disorders observed in arrhythmogenic right ventricular dysplasia. Arch Mal Coeur Vaiss 1984;77:872-9.
7. Mehta D, Odawara H, Ward DE, McKenna WJ, Davies MJ, Camm AJ. Echocardiographic and histologic evaluation of the right ventricle in ventricular tachycardias of left bundle branch block morphology without overt cardiac abnormality. Am J Cardiol 1989;63:939-44.
8. McKenna WJ, Thiene G, Nava A, Fontaliron F, Blomstrom-Lundquist G, Fontaine G, et al. On behalf of the Task Force of the working group myocardial and pericardial disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology, Diagnosis of arrhythmogenic right ventricular dysplasia cardiomyopathy. Br Heart J 1994;71:215-8.
9. Romero J, Mejia-Lopez E, Manrique C, Lucariello R. Arrhythmogenic right ventricular cardiomyopathy (ARVC/D): a systematic literature review. Clin Med Insights Cardiol 2013:7;97-114.
10. Protocols for ECG, SAECG, Holter monitoring, echo and RV-gram. URL: http//www.arvd.org/diagnostics/html.
11. Tandri H, Daya SK, Nasir K, Bomma C, Lima JAC, Calkins H, et al. Normal reference values for the adult right ventricle by magnetic resonance imaging. Am J Cardiol 2006;98:1660-4.
12. Tandri H, Saranathan M, Rodriguez R, Martinez C, Bomma C, Nasir K, et al. Noninvasive detection of myocardial fibrosis in arrhythmogenic right ventricular cardiomyopathy using delayed-enhancement magnetic resonance imaging. J Am Coll Cardiol 2005;45:98-103.
13. Indik JH, Wichter T, Gear K, Dallas WJ, Marcus FI. Quantitative assessment of angiographic right ventricular wall motion in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). J Cardiovasc Electrophysiol 2008;19:39-45.
14. Marcus FI. Prevalence of T-Wave Inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Am J Cardiol 2005;95:1070-1.
15. Marcus FI, Zareba W, Sherrill D. Evaluation of the normal values for signal-averaged electrocardiogram. J Cardiovasc Electrophysiol 2007;18:231-3.
16. Kamath GS, Zareba W, McKenna WJ, Gear K, Sherrill D, Marcus F, et al. Value of signal averaged

electrocardiogram for the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Heart Rhythm 2008;5:S38.

17. Ainsworth CD, Skanes AC, Klein GJ, Gula LJ, Yee R, Krahn AD. Differentiating arrhythmogenic right ventricular cardiomyopathy from right ventricular outflow tract ventricular tachycardia using multilead QRS duration and axis. Heart Rhythm 2006;3:416-3.
18. DePaula SR, Antelmi I, Vincenzi MA, Andre CD, Artes R, Grupi CJ, et al. Cardiac arrhythmias and atrioventricular block in a cohort of asymptomatic individuals without heart disease. Cardiology 2007;108:111-6.
19. Cox MG, van der Smagt JJ, Wilde AA, Wiesfeld AC, Atsma DE, Nelen MR, et al. New ECG criteria in arrhythmogenic right ventricular dysplasia/ cardiomyopathy. Circ Arrhythm Electrophysiol 2009;2:524-30.
20. Marcus F, Zareba W, Calkins H, Towbin JA, Basso C, Bluemke DA. Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: results from the North American Multidisciplinary Study. Heart Rhythm 20.