CASE REPORT

Biventricular Arrhythmogenic Cardiomyopathy: A New Paradigm?

João Augusto,[1] João Abecasis,[2] Victor Gil[2]

Service of Cardiology, Hospital Professor Doutor Fernando Fonseca,[1] Amadora - Portugal
Cardiovascular Unit, Hospital dos Lusíadas,[2] Lisbon - Portugal

Abstract

Arrhythmogenic right ventricular dysplasia is a classic form of chronic myocardial disease with a broad phenotypical spectrum. We report an atypical case of a patient with biventricular arrhythmogenic cardiomyopathy. Although the current diagnosis criteria are the most widely accepted ones, they focus solely on the right ventricular phenotype. The use of late gadolinium enhancement in cardiac magnetic resonance in this patient was essential for the diagnosis and assessment of the left ventricular involvement extent. This tool allows a broader use of current diagnosis criteria for this disease.

Introduction

Arrhythmogenic right ventricular dysplasia / cardiomyopathy (ARVD) consists of the classic form of a chronic, progressive and hereditary myocardial disease that has a broad phenotypic spectrum.[1] The use of the broader term "arrhythmogenic cardiomyopathy" (AC) is now accepted, which also encompasses the variants involving either mainly the left ventricle (LV) or the LV and the right ventricle (RV) - the latter, usually understood as a later form of the disease.[1] The incidence of this disease is 1:2,000 to 1:5,000, and the mean age at diagnosis is approximately 30 years old, constituting an important cause of sudden cardiac death.[2,3]

We report on a patient with ARVD and concomitant LV involvement.

Keywords

Cardiomyopathies; Arrhythmogenic Right Ventricular Dysplasia; Arrhythmias, Cardiac; Magnetic Resonance Imaging; Death, Sudden, Cardiac.

Case report

A 57-year-old male patient with irregular follow-up at a cardiology clinic for 15 years due to complaints of palpitations at exertion was assessed. He only had a history of systemic arterial hypertension, medicated and controlled with bisoprolol and lisinopril, with no other significant personal history or family history. The most recent electrocardiographic exams showed sinus rhythm, left anterior hemiblock pattern, premature ventricular contractions with complete left bundle branch block (LBBB) and superior axis, as well as periods of non-sustained ventricular tachycardia.

The previous complementary examinations included a 24-hour Holter monitoring with a non-sustained ventricular tachycardia (VT) episode with LBBB configuration, with very frequent polymorphic premature ventricular contractions (136/hr). The patient had been submitted to a transthoracic echocardiogram performed 3 years earlier, showing slight impairment of LV systolic function (ejection fraction of 47% according to the biplane Simpson's method) and diffuse hypokinesia; dilated RV also with slight systolic function impairment and apparent asymmetries in the segmental contractility of the inferior wall.

The patient was referred for cardiac magnetic resonance imaging (MRI) (Figure 1), which showed a slightly dilated LV (end-diastolic index volume of 107 mL/m^2), with ejection fraction of 44%; and a slightly dilated RV (end-diastolic index volume of 109 mL/m^2) with an ejection fraction of 39%, with evident dyskinetic areas on the free and diaphragmatic walls (in systole and diastole). There were also extensive areas of late enhancement (fibrosis) on the RV free wall (particularly at the third basal level), as well as on the LV interventricular septum and anterolateral wall, with a mid-myocardial distribution. No areas of adipocyte infiltration were observed in the fat suppression sequences.

Mailing Address: João B. Augusto
Hospital Professor Doutor Fernando Fonseca, IC19. Postal Code: 2720-276, Lisboa - Portugal
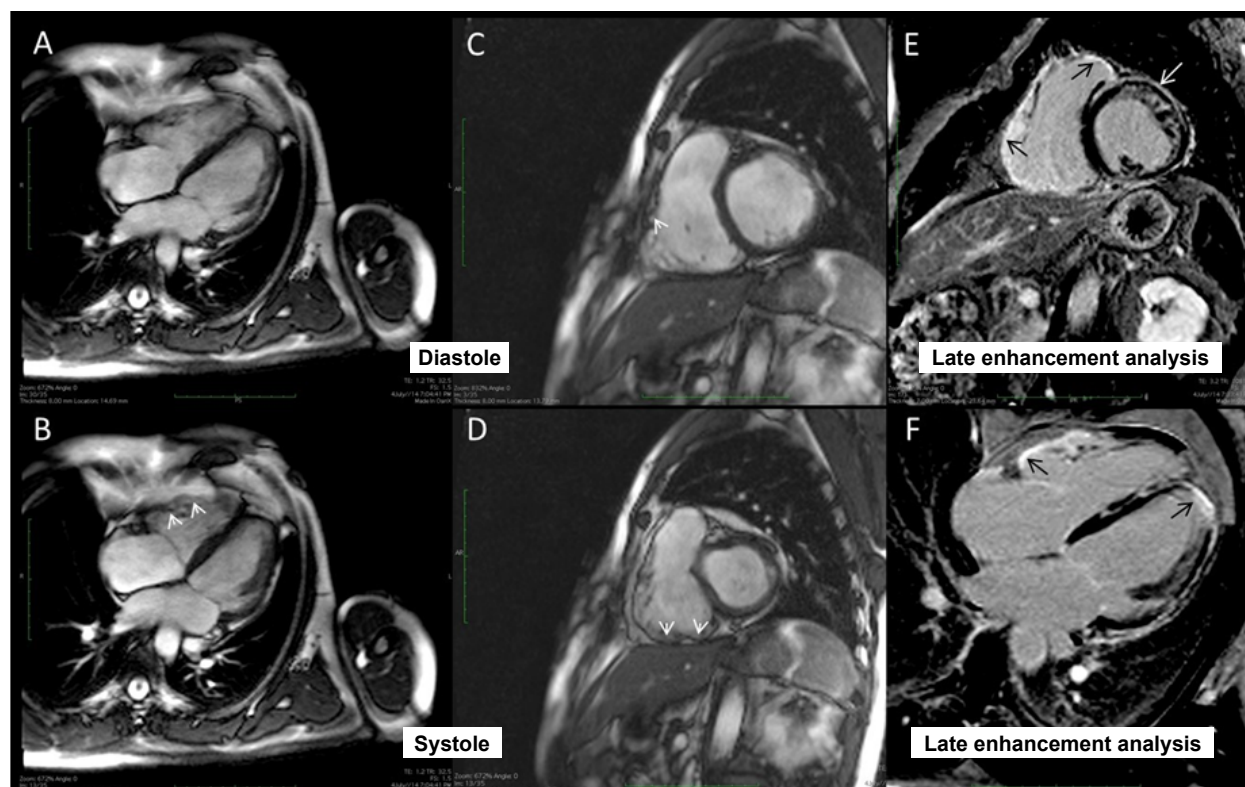E-mail: joao.augusto@hff.min-saude.pt

Figure 1 - Cardiac magnetic resonance imaging. (A to D) Cine-MRI, according to the steady-state free precession sequences. (A and B) long-axis, apical four-chamber view (A, diastole, and B, systole); (C and D) short axis (C, diastole and D, systole). Note marked dyskinesia of the free and diaphragmatic walls of the right ventricle in systole and diastole (arrowheads). (E and F) Gradient echo images - inversion recovery, 10 minutes after gadolinium injection: late enhancement areas (arrows) are visualized on the right ventricular free wall, interventricular septum and left ventricular anterolateral wall, with non-ischemic distribution (mid-myocardial).

The presence of arrhythmogenic cardiomyopathy with biventricular involvement was admitted as the definitive diagnosis. The documentation of several episodes of non-sustained ventricular tachycardia in this context, with biventricular dysfunction, was the reason the patient was referred to receive an implantable cardioverter defibrillator (ICD).

Discussion

Although most patients with ARVD are asymptomatic, palpitations and syncope are common presenting symptoms.[2] A high level of suspicion is essential in cases where these symptoms are related to frequent premature ventricular contractions or VT episodes (sometimes asymptomatic ones), usually with the LBBB configuration (right ventricular origin) and superior axis.[4,5]

The classical diagnosis requires the histological evidence of myocardial replacement by fibrous or fibroadipose tissue, predominantly in the RV;[3,6] however, in the clinical context, the revised diagnostic criteria of the 2010 Task Force are applied.[5]

The definitive diagnosis is based on the presence of two major criteria; one major criterion and two minor criteria; or four minor criteria from six different categories: global or regional structural changes, depolarization abnormalities, repolarization abnormalities, arrhythmias, histological findings, family history / genetic study (Chart 1).

Our case is noteworthy due to the presence of non-sustained VT, premature ventricular contractions with complete LBBB and superior axis pattern, as well as evidence of right ventricular dilatation and dysfunction associated with asymmetry / dyssynchrony of the RV free wall (Figure 1, arrow heads), with two major criteria being met - a definitive diagnosis according to the revised 2010 Task Force criteria. The presence of concomitant left ventricular dysfunction and late enhancement

Chart 1 - Revised 2010 Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD)

1. Global or regional dysfunction and structural alterations

Major	At the two-dimensional echocardiogram:
	- Regional right ventricular akinesis, dyskinesis or aneurysm
	And one of the following (end-diastolic):
	- RVOT PLAX $\geq$ 32 mm (corrected for the body surface area − PLAX/BSA $\geq$ 19 mm/m^2)
	- RVOT PSAX $\geq$ 36 mm (corrected for the body surface area − PLAX/BSA $\geq$ 21 mm/m^2)
	- Or fractional alteration of the area $\leq$ 33%
	At the MRI:
	- Regional right ventricular akinesis, dyskinesis or dyssynchrony in right ventricular contractions
	And one of the following:
	Ratio of right ventricular end-diastolic volume and BSA $\geq$ 110 mL/m^2 (male) or BSA $\geq$ 100 mL / m^2 (female)
	-- Or right ventricular ejection fraction $\leq$ 40%
	At the right ventricular angiography:
	- Right ventricular regional akinesis, dyskinesis or aneurysm
Minor	At the two-dimensional echocardiogram:
	- Right ventricular regional akinesis or dyskinesis
	And one of the following (end-diastolic):
	- RVOT PLAX $\geq$ 29 mm and < 32 mm (corrected for the body surface area − PLAX/BSA $\geq$ 16 mm/m^2 and < 19 mm/m^2)
	- RVOT PSAX $\geq$ 32 mm and < 36 mm (corrected for the body surface area − PLAX/BSA $\geq$ 18 mm/m^2 and < 21 mm/m^2)
	- Or fractional alteration of the area > 33% and $\leq$ 40%
	At the MRI:
	- Regional right ventricular akinesis or dyskinesis or dyssynchrony in right ventricular contraction
	And one of the following:
	- Ratio of right ventricular end-diastolic volume and BSA $\geq$ 100 and < 110 mL/m^2 (man) or $\geq$ 90 and < 100 mL/m^2 (woman)
	- Or
	Right ventricular ejection fraction > 40% and $\leq$ 45%

2. Histological characterization of the ventricular wall

Major	- Residual myocytes <60% in the morphometric analysis (or <50% by estimation) with fibrous replacement of the right ventricular free wall in more than one sample, with or without adipose replacement in myocardial biopsy
Minor	- 60-75% of residual myocytes in the morphometric analysis (or 50-65% by estimation) with fibrous replacement of right ventricular free wall in more than one sample, with or without adipose replacement in myocardial biopsy

3. Ventricular repolarization alterations

Major	- Inverted T waves in V1, V2 or V3 in individuals aged > 14 years in the absence of complete RBBB with QRS $\geq$ 120 ms
Minor	- Inverted T waves in V1 and V2 in individuals aged > 14 years in the absence of complete RBBB with QRS $\geq$ 120 ms or in V4, V5 or V6
	Inverted T waves in V1, V2, V3 and V4 in subjects aged > 14 years in the presence of complete RBBB with QRS $\geq$ 120 ms

Cont. chart 1 - Revised 2010 Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD)	
4. Conduction/depolarization alterations	
Major	- Epsilon wave in leads V1 to V3
Minor	- Duration of QRS terminal activation ≥ 55 ms measured from the S wave nadir to the end of QRS, including R' at V1, V2, V3 in the absence of complete RBBB of the His bundle
	- High-resolution ECG late potentials in more than one of the following three parameters in the absence of QRS ≥ 110 ms on the standard 12-lead ECG:
	- Duration of filtered QRS (fQRS) ≥ 114 ms
	- QRS terminal duration < 40 μV (low amplitude signal duration) ≥ 38 ms
	- Root mean square of the potential in the 40 ms terminals of ventricular activation (MRIS40 - mV) ≤ 20 μV
5. Arrythmias	
Major	- Sustained or non-sustained ventricular tachycardia with complete LBBB morphology with superior axis (QRS negative or undetermined in II, III, aVF and positive in aVL)
Minor	- Sustained or non-sustained ventricular tachycardia with right ventricular outflow tract configuration, complete LBBB morphology with inferior axis (QRS positive in II, III and aVF and negative in aVL) or of indeterminate axis
	- > 500 ventricular extrasystoles in the 24-hr Holter monitoring
6. Family history	
Major	- Confirmed ARVD in a first-degree relative meeting the Task Force criteria
	- ARVD confirmed by histopathology at the autopsy or surgery in first-degree relative
	- Identification of pathogenic mutation categorized as associated or likely to be associated with ARVD* in a patient undergoing evaluation
Minor	- History of ARVD in a first-degree relative in whom it is not possible or the feasibility of confirming the presence of Task Force criteria is difficult
	- Sudden cardiac death (age < 35 years) due to suspected ARVD in first-degree relative
	- ARVD confirmed by histopathology or according to the current Task Force criteria in second-degree relative

* A pathogenic mutation is understood as a DNA change associated with ARVD, which alters or is expected to alter a coded protein, not being observed or being rare in a control population without ARVD, and which alters or is predicted to alter the protein function or structure, or that has shown an association with the phenotype of the pathology in a family tree. RVOT: right ventricular outflow tract; PLAX: parasternal long axis; MRI: magnetic resonance imaging; BSA: body surface area; PSAX: parasternal short axis; RBBB: right bundle branch block; ECG: electrocardiogram; LBBB: left bundle branch block. Source: adapted from Marcus et al.[5]

not restricted to the RV (Figure 1, arrows) is a finding compatible with biventricular involvement in the context of this cardiomyopathy.

It is important to emphasize that these diagnostic criteria refer to the ARVD, with or without LV involvement. However, LV involvement has been increasingly described, because of the development of several complementary diagnostic means, such as the cardiac MRI.[7] It is worth mentioning that, in some series, biventricular involvement reaches 70%.[5]

This case is noteworthy not only for the presence of biventricular dilatation and dysfunction, but also for the obvious presence of late enhancement with a non-ischemic pattern in both ventricles; this last finding has a sensitivity of 66% and a specificity of 100% for the diagnosis of this entity.[8] Particularly relevant is the use of the late enhancement criterion for the supposed evaluation of the LV involvement extent in some published series and case reports, when it does not integrate the current Task Force diagnostic items.[9] In fact,

the current diagnostic criteria for this cardiomyopathy, although being the most unanimous and accepted ones, are based on data from a relatively small series of patients, in which the respective diagnostic sensitivities and specificities of each criterion were evaluated.

The main therapeutic goal in these patients is the prevention of malignant arrhythmias and, consequently, of sudden cardiac death, which is the most feared complication. The ICD plays a key role in the secondary prevention of sudden cardiac death, being associated with longer survival in these patients.[10] Patients with biventricular involvement and good functional status are potential candidates for ICD implantation, even in the absence of ventricular arrhythmias. However, how biventricular involvement in this setting may impact on the follow-up, the therapeutic approach, referral for ICD implantation, and patient prognosis should remain to be established.

Conclusions

Although the current diagnosis criteria are the most widely accepted ones, they focus mainly on the right ventricular phenotype. The use of late enhancement in cardiac magnetic resonance in this patient was essential for the diagnosis and assessment of the left ventricular involvement extent. This tool allows a broader use of the current diagnosis criteria for this disease.

Author contributions

Conception and design of the research: Augusto J, Abecasis J. Writing of the manuscript: Augusto J, Abecasis J. Critical revision of the manuscript for intellectual content: Abecasis J, Gil V.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

References

1. Sem-Chowdhry S, Morgan RD, Chambers JC, McKenna WJ. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. Annu Rev Med. 2010;61:233-53.

2. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. 2004;110(4):1879-84.

3. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):e247-346.

4. Niroomand F, Carbucicchio C, Tondo C, Riva S, Fassini G, Apostolo A, et al. Electrophysiological characteristics and outcome in patients with idiopathic right ventricular arrhythmia compared with arrhythmogenic right ventricular dysplasia. Heart. 2002;87(1):41-7.

5. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/

dysplasia: proposed modification of the task force criteria. Circulation. 2010;121(13):1533-41.

6. Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2001;38(7):1773-81.

7. Abecasis J, Masci PG, Aquaro GD, Pingitore A, De Marchi D, Lombardi M. Arrhythmogenic biventricular dysplasia? Rev Port Cardiol. 2009;28(12):1459-63.

8. Tandri H, Saranathan M, Rodriguez ER, 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(1):98–103.

9. Satoh H, Sano M, Suwa K, Saitoh T, Nobuhara M, Saotome M, et al. Distribution of late gadolinium enhancement in various types of cardiomyopathies: Significance in differential diagnosis, clinical features and prognosis. World J Cardiol. 2014;6(7):585-601.

10. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127(3):e283-e352.