British Journal of Medicine & Medical Research
18(4): 1-8, 2016, Article no.BJMMR.28394
ISSN: 2231-0614, NLM ID: 101570965

SCIENCEDOMAIN *international*
www.sciencedomain.org

Increasing Role of Magnetic Resonance in Diagnosis and Prognosis of Arrhythmogenic Right Ventricle Dysplasia/Cardiomyopathy

Sílvia Aguiar Rosa[1*], Susana Castela[2], Pedro Matos[2], Manuel Nogueira da Silva[3] and Nuno Jalles Tavares[4]

[1]Department of Cardiology, Santa Marta Hospital, Lisbon, Portugal.
[2]Department of Cardiology, CUF Infante Santo Hospital, Lisbon, Portugal.
[3]Department of Cardiology, CUF Descobertas Hospital, Lisbon, Portugal.
[4]Department of Radiology, CUF Infante Santo Hospital, Lisbon, Portugal.

Authors' contributions

This work was carried out in collaboration between all authors. Author SAR collected clinical data, managed the literature searches and wrote the first draft of the manuscript. Author SC preformed MRI scan. Authors SC, PM and NJT analyzed and interpreted MRI images. Author MNS contributed for electrocardiogram and arrhythmias analysis. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/28394
Editor(s):
(1) S. U. Fuhong, ICU Laboratory, Erasme Hospital, Free University Brussels, Brussels, Belgium.
Reviewers:
(1) Maddury Jyotsna, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, India.
(2) Lalit Gupta, Rajiv Gandhi Super-Speciality Hospital, India.
(3) Osman Beton, Cumhuriyet University, Sivas, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/16592

Case Study

Received 17th July 2016
Accepted 13th October 2016
Published 18th October 2016

ABSTRACT

A 33-year-old woman with previous diagnosis of asymptomatic frequent premature ventricular complexes (PVC), without documented structural disease in echocardiography. She presented recently with palpitations and dizziness. Another echocardiogram was performed suggesting for the first time right ventricle (RV) dilation and possible hypokinesia of RV apex. Electrocardiogram showed T-wave inversion in V1-V2 and Epsilon wave in V1. Holter documented 2869 polymorphic isolated PVC. Cardiovascular magnetic resonance (CMR) showed moderate RV dilation (end-diastolic volume of 125 ml/m^2), RV systolic dysfunction (RV ejection fraction 33%) with RV free wall hypokinesia, a focal area of dyskinesia ("buldging") in RV outflow tract and trabecular disarray.

**Corresponding author: E-mail: silviaguiarosa@gmail.com;*

There was no evidence of intra-myocardial fat. Positive Late gadolinium enhancement was evident in RV free wall and RV outflow tract.
Genetic test showed heterozygous desmoglein-2 (DSG2) mutation.
The patient fulfilled criteria for Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy (ARVD/C).
Diagnosis of ARVD/C can be challenging, requiring closer follow up and evaluation of multiple parameters. CMR is the imaging method of choice for diagnostic, structural evaluation and risk stratification.

Keywords: Arrhythmogenic right ventricular dysplasia /cardiomyopathy; cardiovascular magnetic resonance; Late gadolinium enhancement (LGE).

ABBREVIATIONS

RV : Right ventricle
PVC : Premature ventricular complexes
CMR : Cardiovascular magnetic resonance
ARVD/C : Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy
ECG : Electrocardiogram
DSG2 : Desmoglein-2

1. INTRODUCTION

Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy (ARVD/C) is characterized by progressive fibrofatty replacement primarily of right ventricular myocardium. The clinical presentation is characterized by arrhythmia, heart failure and sudden death.

Diagnosis criteria include several parameters such as right ventricular (RV) dysfunction, structural alterations, tissue characterisation, electrical abnormalities, family history and genetic mutations. Cardiovascular magnetic resonance (CMR) has emerged as the imaging modality of choice for diagnostic.

The present paper reported a well documented case of ARVD/C, emphasising the role CMR in diagnosis and risk stratification.

2. CASE REPORT

33-year-old woman with frequent premature ventricular complexes (PVC) for 15 years, asymptomatic, without regular medication. During this period echocardiograms were persistently unremarkable. Patient had no relevant family medical history. Since the beginning of pregnancy, the patient presented palpitations and dizziness, including at rest. Another echocardiogram was performed, suggesting for the first time RV dilation, with hypokinesia of RV apex. Electrocardiogram (ECG) showed sinus rhythm, T-wave inversion in V1 and V2 with distinct small waves after the QRS complex in V1 – Epsilon wave (Fig. 1). Twenty four hours Holter recording documented 2869 polymorphic isolated PVC and one triplet (2.6% of registry). After childbirth a CMR, with gadolinium administration, was performed in a 3 Tesla scanner. Quantitative analysis of right and left ventricle volumes was performed over short axis images, with 10 slices (8 mm thickness, 2mm gap) encompassing the entire ventricular cavities, using a breath-hold steady state free precession (SSFP) sequence, gated to the electrocardiogram. SSFP images were also obtained in two, four chamber and long axis views and axial and oblique right-sided planes. Dark blood T1 weighted (fat-suppressed and non-fat-suppressed) images in short axis were acquired with double inversion recovery blood suppression and short TI inversion recovery (STIR) sequence. Delayed gadolinium enhancement images were obtained in short and long axis, 10 minutes after intravenous administration of 0.2 mmol/Kg of gadolinium, using phase sensitive inversion recovery (PSIR) reconstruction.

CMR documented RV dilation (end-diastolic volume of 125 ml/m^2), RV systolic dysfunction (RV ejection fraction 33%), hypokinesia of RV free wall and RV outflow tract, with focal area of dyskinesia ("bulging") and trabecular disarray in RV free wall (Fig. 2). There was no evidence of intra-myocardial fat in dark blood images. No changes were documented in left ventricle. Late gadolinium enhancement (LGE) was present in RV free wall and RV outflow tract (Fig. 3).

Genetic test showed heterozygous desmoglein-2 (DSG2) mutation (c.1003A>G).

The patient fulfilled criteria for ARVD/C, since she presented three major criteria (Epsilon wave in ECG, major criteria in CMR and genetic

mutation) and two minor criteria (> 1000 PVC/24 hours and inverted T waves in V1 and V2) (Table 1).

3. DISCUSSION

ARVD/C is a genetically determined disease with predominantly autosomal dominant inheritance with incomplete penetrance due to a mutation in desmoplakin, plakoglobin, plakophilin-2, desmoglein-2, desmocollin-2, transforming growth factor beta-3 or ryanodine receptor [1,2] , with an estimated prevalence of 1 in 2000 to 5000 individuals and a ratio male/female of 2.7/1.0. [3,4] The disease is characterized by fibrofatty replacement primarily of right ventricular myocardium [4,5].

The most common feature is only segmental right ventricular disease, but evolution to more diffuse right and left ventricular involvement may occur [6].

This progressive replacement is responsible for the clinical presentation and patients may present themselves with arrhythmia, heart failure and sudden death. ARVD/C is an important cause of sudden death among young people, particularly during strenuous activity [7].

The gold standard for diagnosis is the histopathologic evidence of transmural fibrofatty replacement of right ventricular myocardium, but diagnosis based on biopsy is difficult due to the patchy distribution [6]. In this context diagnosis should be based on multiple criteria including clinical demonstration of structural, functional, and electrophysiological abnormalities [6,8]. McKenna and co-workers presented diagnostic criteria in 1994, revised and updated in 2010, and proposed that the diagnosis of ARVD/C is fulfilled by the presence of two major criteria or one major plus two minor criteria or four minor criteria (Table 1) [6,2].

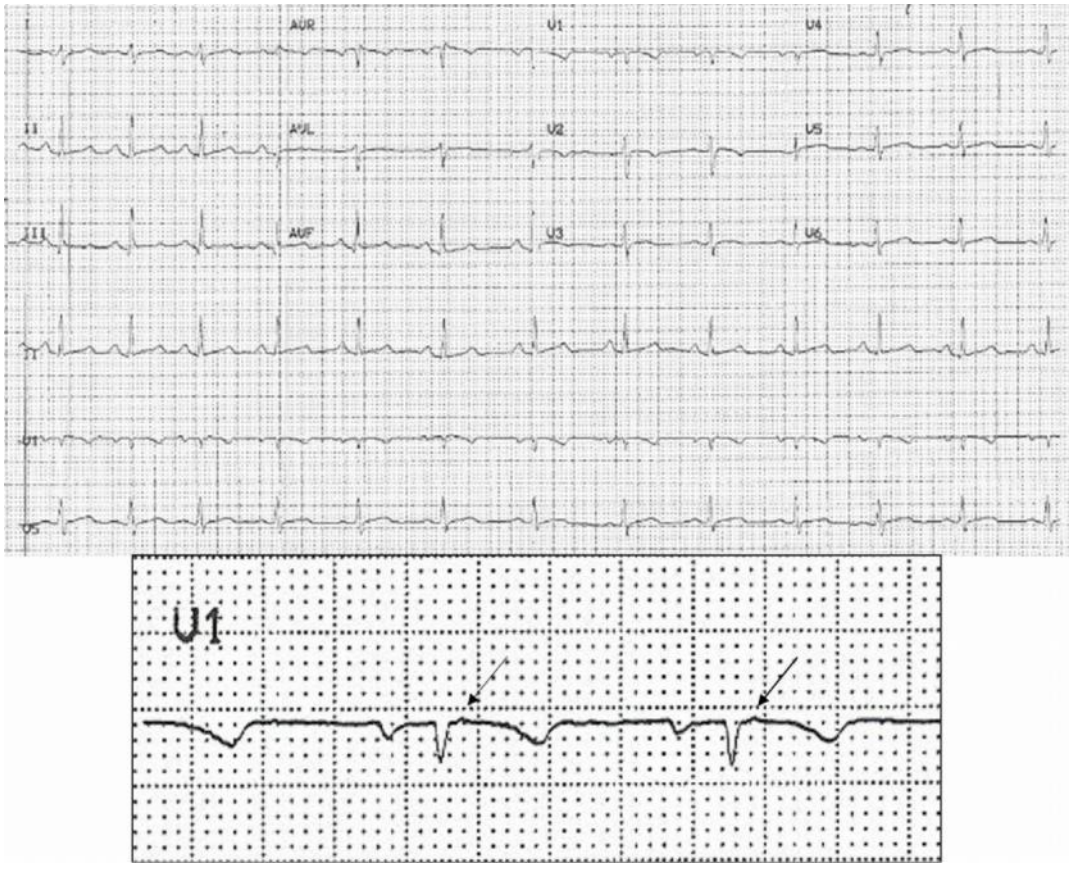

Fig. 1. Electrocardiogram documented an Epsilon wave in V1 (arrow) and T wave inversion in V1 and V2

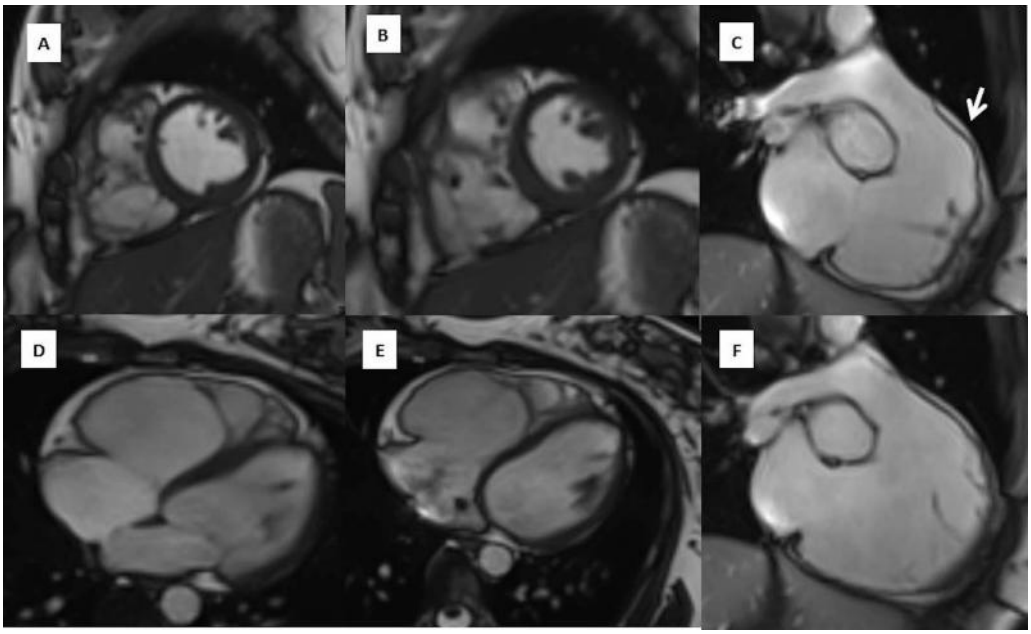

Fig. 2. Cardiovascular Magnetic Resonance - Steady state free precession imaging documented right ventricular (RV) dilation, dyskinesia and trabecular disarray of RV free wall and outflow tract in short axis view (A and B) and four chamber views (D and E). Oblique RV outflow tract view (C and F) shows focal area of dyskinesia - "bulging" (arrow) in RV free wall

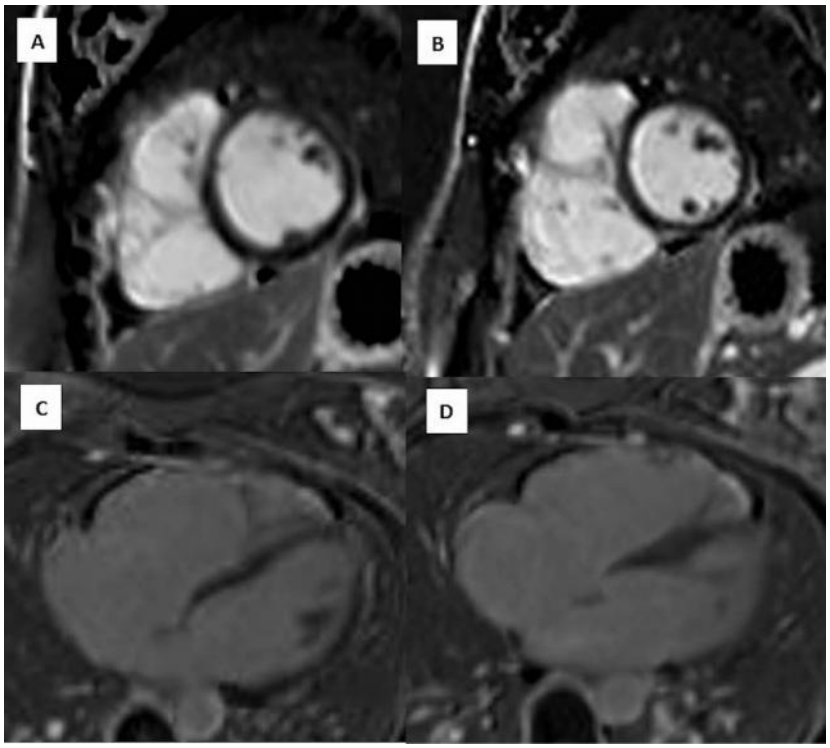

Fig. 3. Late gadolinium enhancement (LGE) using phase sensitive inversion recovery (PSIR) reconstruction, acquired 10 minutes after gadolinium intravenous administration. LGE is evident in right ventricular free wall and outflow tract, in short axis view (A and B) and four chamber view (C and D)

Table 1. Proposed diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy

Right ventricular dysfunction and structural alterations
Major
2D Echocardiography criteria
Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following measured at end diastole:
- PLAX RVOT ≥ 32 mm (PLAX/ BSA ≥ 19 mm/m2), or
- PSAX RVOT ≥ 36 mm (PSAX/ BSA ≥ 21 mm/m2), or
- Fractional area change ≤ 33%
Cardiac Magnetic Resonance criteria
Regional RV akinesia or dyskinesia or dysynchronous RV contraction and 1 of the following:
- RV EDV/BSA ≥ 110 mL/m2 (male) or ≥ 100 mL/m2 (female)
- RV ejection fraction ≤ 40%
Right ventricle angiography criteria
Regional RV akinesia, dyskinesia, or aneurysm
Minor
2D Echocardiography criteria
Regional RV akinesia or dyskinesia or dysynchronous RV contraction AND 1 of the following measured at end diastole:
- PLAX RVOT ≥ 29 to <32 mm (PLAX/ BSA ≥16 to < 19 mm/m2), or
- PSAX RVOT ≥32 to <36 mm (PSAX/ BSA ≥18 to < 21 mm/m2), or
- Fractional area change > 33% ≤ 40%
Cardiac Magnetic Resonance criteria
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
- RV EDV/ BSA ≥100 to 110 mL/m2 (male) or ≥ 90 to 100 mL/m2 (female)
- RV ejection fraction >40 to ≤ 45%
Tissue characterisation
Major
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
Minor
Residual myocytes 60% to 75% by morphometric analysis (or 50% to 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
Repolarisation abnormalities
Major
Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 yrs of age (in the absence of complete RBBB QRS ≥ 120 ms)
Minor
Inverted T waves in V1 and V2 in individuals >14 yrs of age (in the absence of complete RBBB) or in V4, V5, and V6
Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of a complete RBBB
Depolarisation/conduction abnormalities
Major
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in the right precordial leads (V1 - V3)
Minor
Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRSd of ≥ 110 msec on standard ECG:
- Filtered QRS duration (fQRS) ≥ 114 msec
- Duration of terminal QRS < 40 microV ≥ 38 ms
- Root-mean-square voltage of terminal 40 ms ≤20 micro V
Terminal activation duration ≥ 55 ms measured from the nadir of the S-wave until the end of all depolarization deflections (including R') in V1, V2, or V3

Arrhythmias
Major
Nonsustained or sustained VT of LBBB morphology with superior axis
Minor
Nonsustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis or of unknown axis
> 500 PVCs per 24 hours on Holter monitoring
Family history
Major
Major
ARVC in first degree relative who meets Task Force Criteria ARVC confirmed pathologically at autopsy or surgery in
first degree relative.
Identification of pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation
Minor
History of ARVC in first degree relative in whom it is not possible to determine whether the family member meets Task Force Criteria Premature sudden death (<35 years of age) due to suspected ARVC in a first degree relative
ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

Adapted from McKenna et al[6] and Marcus et al.[9]

ARVC Arrhythmogenic Right Ventricular Cardiomyopathy, BSA body surface area, ECG electrocardiogram, EDV end-diastolic volume, LBBB left bundle branch block, PLAX parasternal long axis, PSAX parasternal short axis, RV right ventricular, RVOT right ventricular outflow tract, SAECG signal-averaged electrocardiogram, VT ventricular tachycardia

As shown in our case report, the cardiac investigation may be unremarkable in the concealed phase of ARVD/C, and electrical abnormalities precede structural changes [9]. Therefore a continuous follow up is needed to diagnose the development of new clinical features in order to reach the correct diagnosis.

Our patient presented Epsilon wave in ECG, which is the result of modification in electrical activation, as well as a T-wave inversion in V1 and V2 which is the result of modification in repolarization secondary to anatomic damage present in ARVD/C. Nasir et al. [10] showed an Epsilon wave prevalence of 53% in diffuse ARVD/C and 15% in localized ARVD/C. T-wave inversion in V1 through V3 was observed in 85% of ARVD/C patients and, as In this particular study, T-wave inversion only in V1 and V2 was observed in 10% of patients.

Echocardiography and CMR are the Imaging modalities commonly used to diagnose and evaluate ARVD/C. However, echocardiography has significant limitations in ARVD/C assessment due to RV complex geometry and CMR has emerged as the imaging modality of choice. CMR allows more detailed morphological and functional evaluation and also tissue characterization. Using the diagnostic criteria showed in Table 1, major CMR criteria have a specificity of 95% and a sensitivity of 68 to 76% and minor criteria have a sensitivity of 79 to 89% and a specificity of 85 to 97% [11].

Common findings in CMR include RV dilation, RV diastolic/systolic dysfunction and focal wall motion abnormalities such as localized area of akinesia (lack of motion), dyskinesia (the segment of myocardium bulges outward in systole) and regional dysynchronous movement (peak contraction occurring at different times). These abnormalities are more commonly seen in RV inflow / outflow tract and apico-lateral region, but can also be noticed in subtricuspid region and basal RV free wall [11,12,13]. Regional dysfunction is observed in most of the patients, even in the presence of normal global function [13]. Trabecular disarray and wall thinning are common [11].

The identification of myocardial fat by CMR is challenging and has lower sensitivity, since areas of adipose infiltration are small and focal. Furthermore, Tandri et al. [14] showed that this finding may not be specific and it is the least reproducible CMR parameter. Even double inversion-recovery fast spin-echo sequences alone and combined with fat suppression are limited in spatial resolution for detecting intra-myocardial fat [15]. Therefore, as LGE is a well validated technique for assessment of myocardial fibrosis, this is the preferred approach for RV tissue characterization and identification

of fibro-adipose replacement [11,12]. In addition there is a high degree of correlation between LGE and RV biopsy, RV function and inducible ventricular arrhythmias on electrophysiologic study, making LGE an important tool in the management of these patients, including risk stratification [16]. In a previous study with ARVD/C associated mutation carriers without prior sustained ventricular arrhythmias, te Riele et al. [17] demonstrated that a combined strategy using electrocardiography, Holter and CMR identified patients at high risk for arrhythmias. Patients with both electrical and CMR abnormalities had a higher incidence of arrhythmic events, suggesting that patients with this clinical profile might eventually benefit from prophylactic implantable cardioverter-defibrillator.

4. CONCLUSION

In conclusion, diagnosis and follow up of ARVD/C require a rigorous evaluation of multiple parameters, particularly electrical and structural assessment, being CMR the imaging modality of choice for diagnostic and risk stratification. LGE is emerging as a very relevant data for diagnosis and prognosis, substituting the search for intramyocardial fat. In this context, we can postulate that maybe LGE could be included in diagnostic criteria for ARVD/C.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Rampazzo A, Nava A, Malacrida S, et al. Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet. 2002;71:1200–6.
2. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the task force criteria. Circulation. 2010;121(13):1533-41.
3. van der Wall EE, Bootsma M, Wellens HJ, Bax JJ, de Roos A, Schalij MJ. Arrhythmogenic right ventricular dysplasia/ cardiomyopathy: New avenues for diagnosis and treatment. Neth Heart J. 2003;11(1):15-27.
4. Pezawas T, Stix G, Kastner J, et al. Ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy: clinical presentation, risk stratification and results of long-term follow-up. Int J Cardiol. 2006;107(3):360-8.
5. Sen-Chowdhry S, Lowe MD, Sporton SC. Arrhythmogenic right ventricular cardiomyopathy: Clinical presentation, diagnosis and management. Am J Med. 2004;117(9):685-95.
6. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. 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. Br Heart J. 1994;71(3):215-8.
7. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988;318:129–33.
8. Marcus FI, Zareba W, Calkins H, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: results from the North American multidisciplinary study. Heart Rhythm. 2009;6(7):984-92.
9. Gomes J, Finlay M, Ahmed AK, et al. Electrophysiological abnormalities precede overt structural changes in arrhythmogenic right ventricular cardiomyopathy due to mutations in desmoplakin-A combined murine and human study. Eur Heart J. 2012;33:1942–53.
10. Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/ cardiomyopathy according to disease severity: A need to broaden diagnostic criteria. Circulation. 2004;110(12):1527-34.

11. te Riele AS, Tandri H, Bluemke DA. Arrhythmogenic right ventricular cardiomyopathy (ARVC): Cardiovascular magnetic resonance update. J Cardiovasc Magn Reson. 2014;16:50.
12. Jain A, Tandri H, Calkins H, et al. Role of cardiovascular magnetic resonance imaging in arrhythmogenic right ventricular dysplasia. J Cardiovasc Magn Reson. 2008;10:32.
13. Tandri H, Macedo R, Calkins H, et al. Multidisciplinary study of right ventricular dysplasia investigators. Role of magnetic resonance imaging in arrhythmogenic right ventricular dysplasia: Insights from the North American arrhythmogenic right ventricular dysplasia (ARVD/C) study. Am Heart J. 2008;155(1):147-53.
14. Tandri H, Castillo E, Ferrari VA, et al. DA. Magnetic resonance imaging of arrhythmogenic right ventricular dysplasia: Sensitivity, specificity, and observer variability of fat detection versus functional analysis of the right ventricle. J Am Coll Cardiol. 2006;48(11):2277-84.
15. Castillo E, Tandri H, Rodriguez ER, et al. Arrhythmogenic right ventricular dysplasia: *Ex vivo* and *in vivo* fat detection with black-blood MR imaging. Radiology. 2004; 232(1):38-48.
16. Tandri H, Saranathan M, Rodriguez ER, et al. Noninvasive detection of myocardial fibrosis in arrhythmogenic right ventricular cardiomyopathy using delayed-enhance-ment magnetic resonance imaging. J Am Coll Cardiol. 2005;45:98–103.
17. te Riele AS, Bhonsale A, James CA, et al. Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol. 2013;62(19):1761-9.

© 2016 Rosa et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16592