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Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Mimics: The Knot Unravelled By Cardiovascular Magnetic Resonance

Keywords:

Arrhythmogenic Right Ventricular Cardiomyopathy; Magnetic Resonance Imaging; Heart; Cardiomyopathies; Echocardiography

Abbreviations:

Arrhythmogenic right ventricular cardiomyopathy (ARVC); cardiovascular magnetic resonance (CMR); right ventricle (RV); right ventricular end-diastolic volume (RVEDV); right ventricular end-systolic volume (RVESV); right ventricular stroke volume (RVSV); right ventricular ejection fraction (RVEF); left ventricle (LV); left ventricular ejection fraction (LVEF); left ventricular end-diastolic volume (LVEDV); left ventricular end-systolic volume (LVESV); implantable cardioverter defibrillator (ICD); sudden cardiac death (SCD); Task Force Criteria (TFC); late gadolinium enhancement (LGE); body surface area (BSA); transthoracic echocardiogram (TTE); ischemic heart disease (IHD); atrial septal defect (ASD); arrhythmogenic left ventricular cardiomyopathy (ALVC); left ventricular non compaction (LVNC).

Introduction:

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare genetic disease, with variable penetrance [1]. First described in 1736 by Giovanni Maria Lancisi in "De Motu Cordis et Aneurysmatibus" [2], it was initially thought to involve primarily the right ventricle (RV), with partial or total absence of the RV musculature and fibro-fatty replacement [3-4], but recent evidence showed that in up to 70% of cases there is also left ventricular (LV) involvement [5-7]. Clinical symptoms are often heterogeneous and non-specific, including palpitations, syncope and atypical chest pain, hence representing a diagnostic challenge. ARVC can lead to biventricular heart failure and sudden cardiac death (SCD), which represents the first manifestation of the disease in up to 20% of cases [8]. Implantable Cardioverter Defibrillator (ICD) decreases the risk of SCD, so a correct diagnosis is crucial. The diagnosis of ARVC is based on the 2010 Task Force Criteria (TFC) [9], which recommend a multi-parametric approach that takes into account echocardiographic, electrocardiographic and histologic abnormalities, documented ventricular arrhythmia and family history. Imaging criteria for ARVC subtend potential diagnostic pitfalls of which the clinician needs to be aware: normal variants mischaracterized as ARVC, such as chest wall deformity and non-ARVC fatty infiltration (obesity, post-myocardial infarction), and pathologic conditions mimicking ARVC, such as myocarditis, sarcoidosis and pre-tricuspid shunts, which are commonly referred to as ARVC mimics [10]. Cardiovascular Magnetic Resonance (CMR) as part of the 2010 TFC is increasingly used in clinical practice in patients with suspected ARVC in the context of a multi-modality imaging assessment. The aim of our study was to assess the diagnostic role of CMR in patients referred for suspected ARVC and its ability to identify ARVC mimics, and to explore its additional clinical impact.

Materials and methods:

We retrospectively analysed the CMR registry data from the year 2014 (January to December) of a UK tertiary centre, to identify consecutive patients referred for suspected ARVC. Clinical, ECG and echocardiographic data were collected from clinical records. CMR was performed on a 1.5 T scanner (Magnetom Avanto, Siemens Medical Solutions, Enlargen, Germany) and all patients underwent a CMR protocol including the left ventricular (LV) and right ventricular (RV) anatomy, cine and late gadolinium enhancement (LGE) images. Cine images were performed using a steady-state free-precession sequence in the 4-chamber, 3-chamber and 2-chamber long-axis view, followed by a stack of short-axis slice from base to apex; typical image parameters

were TR 38 ms, TE 1.07 ms, flip angle 80°, bandwidth 930 Hz/Px, voxel size 2.0x2.0.8.0mm, slice thickness 8 mm, inter-slice gap 0 mm. Additional RVOT cine images were obtained, followed by a stack of axial views (slice thickness 5mm, inter-slice gap 5mm) through the RVOT from the pulmonary valve to the RV diaphragmatic wall. LGE images were obtained 15-20 minutes after intravenous administration of 0.1 mmol/Kg of gadobutrol (Gadovist 1.0 mmol/ml, Bayer-Schering, Berlin, Germany) in identical planes to the long- and short-axis cine images, using an inversion recovery segmented gradient echo sequence. Typical image parameters were TR 700 ms, TE 3.15 ms, flip angle 25°, slice thickness 8.0 mm, interslice gap 0 mm, bandwidth 140 Hx/Px, voxel size 2.0x1.5x8.0 mm. The inversion time was progressively optimized to null normal myocardium (typical values, 250–350 ms). Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate. According to 2010 Task Force Criteria [9], CMR criteria were defined as *major* in the presence of regional RV akinesia/dyskinesia/dyssynchronous contraction, associated with ratio of right ventricular end-diastolic volume (RVEDV) to body surface area (BSA) ≥110 ml/m^2 (male) or ≥100 ml/m^2 (female), or RV ejection fraction (RVEF) ≤40%; *minor* criterion was defined as the presence of regional RV akinesia/dyskinesia/dyssynchronous contraction, associated with ratio of RV end-diastolic volume (RVEDV) to body surface area (BSA) 100-109 ml/m^2 (male) or 90-99 ml/m2 (female), or RV ejection fraction (RVEF) 40%-45% . Body surface area was calculated using the Du Bois method. The study was reviewed by the local Institutional Research and Innovation Department and in view of its retrospective design a formal ethical approval was waived.

Statistical analysis:

Continuous and categorical variables were expressed as mean±SD and n (%), respectively. Continuous data were compared by using the 2-tailed unpaired t test or by using the Mann-Whitney U test. Categorical variables were compared by using the chi-square test or Fisher exact test, as appropriate. A p-value of <0.05 was considered statistically significant; a Bonferroni-corrected p-value was used for comparison > 2 groups. Comparisons between more than two groups were assessed using the Kruskall-Wallis test, using Dunn's test for *post hoc* comparison. Data were analysed with SPSS® version 23 (IBM®).

Results:

Out of 2,481 scans performed in our CMR centre between Jan-Dec 2014, we identified 124 patients (5%) (56% male, mean age 41±16 years, age range 17-78 years) referred for suspected ARVC. Patients were referred with suspected ARVC/D on the basis of symptoms, family history of ARVC and/or SCD, abnormal ECG or abnormal transthoracic echocardiogram (TTE). Eighty-five patients (69%) were symptomatic: history of palpitations/arrhythmias was reported in 53 patients (43%), syncope with no documented arrhythmia in 26 (21%) and both history of arrhythmia and syncope in 6 patients (5%), while thirty-nine patients (31%) were asymptomatic, with an abnormal ECG and/or TTE found incidentally during school or competitive sport pre-participation screening or pre-operatively. ECG data were available in 65 patients (52%): 53/65 patients (82%) had abnormal ECG, most commonly T-wave inversion in leads V1-V3. Echocardiographic data were available in 96 patients (77%): 26/96 patients (27%) had evidence of abnormal RV on echocardiogram. Family history of SCD was reported in 16 patients (13%), 5 patients (4%) had family history of ARVC and one patient (1%) had family history of both SCD and ARVC (**table 1**).

CMR Findings:

Biventricular volumes and function were overall preserved: mean LV ejection fraction (LVEF) was 61±8%, mean LV end-diastolic volume (LVEDV) was 83±24 ml/m^2 and mean LV end-systolic volume (LVESV) was 34±19 ml/m^2; mean RV ejection fraction (RVEF) was 58±8%, mean RVEDV 84±23 ml/m2 and mean RV end-systolic volume (RVESV) was 36±15 ml/m^2. Thirteen patients (10%) had evidence of LGE. Based on CMR findings, a pathologic substrate was found in 36 patients (29%): ischemic heart disease (IHD) was found in 5 patients (4%) and non-ischemic heart disease in 10 (8%); 5 patients (4%) met CMR imaging criteria for ARVC (**Figure 1A, B, C and D**), of which one had findings consistent with ALVC, and sixteen patients (13%) were ARVC mimics. A structurally normal heart was found in 82 patients (66%) and non-specific findings (mild non-specific regional wall motion abnormalities) in 6 (5%). CMR findings are listed in **Table 2**. Echocardiographic data were available in 96 patients (77%). TTE and CMR findings agreed in 49 patients (51%); CMR provided an entirely new diagnosis in 22 patients (22%) and found a structurally normal heart in 20 patients (21%) who had abnormal findings on TTE. One patient (1%) was identified as ARVC mimics on TTE, as compared to 12 (13%) identified on CMR (p=0.01).

ARVC mimics:

Sixteen patients (13%) were found to have ARVC mimics on CMR. Six patients had normal variant mischaracterized as ARVC: one patient had a pectus excavatum (**Figure 2A and B**) and five had findings consistent with athlete's heart. Ten patients had pathologic conditions mimicking ARVC: cardiac sarcoidosis (n=1), myocarditis (n=1), RV myocardial infarction (n=1), partial congenital absence of pericardium (n=1) (**Figure 2C and D**); 3 patients were diagnosed with left ventricular non compaction (LVNC) and 3 with pre-tricuspid left to right shunting (2 atrio-ventricular septal defect, ASD, and 1 partial anomalous venous return) (**Figure 3**). There was no significant difference in clinical, ECG and TTE characteristics between patients with structurally normal hearts on CMR and those with ARVC and ARVC mimics, and between ARVC and ARVC mimics and the remaining population (Table 1). RVEDV and RV stroke volume (SV) were significantly higher in patients with ARVC (RVEDV p=0.013, RVSV p=0.013) and ARVC mimics (RVEDV p=0.007, RVSV p=0.012), as compared to those with structurally normal hearts. There was no significant difference in RV volumes and function in patients with ARVC and ARVC mimics, while LVESV was significantly larger in patients with ARVC. When comparing patients with ARVC and ARVC mimics (n=21) and the remaining population (n=103), there was no significant difference in clinical, ECG and TTE characteristics while biventricular volumes and RV stroke volume were significantly higher in patients with ARVC and ARVC mimics (RVEDV 79 *vs* 103 ml/m2, p=0.001; RVESV34 *vs* 47 ml/m2, p=0.018, RVSV 46 *vs* 56, p=0.001)(Tabel 2).

Discussion:

Arrhythmogenic right ventricular cardiomyopathy is a rare disease, with variable penetrance and prognosis. Given the implications of such a diagnosis, the 2010 Task Force Criteria (TFC) recommended a multi-parametric approach, comprehensive of imaging findings, family history, arrhythmias, ECG and histologic abnormalities [9]. The symptoms of the disease are non-specific (chest pain, palpitations) and overlap with other cardiomyopathies, thus not being helpful for a definite diagnosis [3,4,7,8]. It is well established that the diagnosis of ARVC cannot rely on imaging findings alone, as imaging is subject to diagnostic pitfalls, such as normal variants mischaracterized for ARVC (i.e. athlete's heart) or pathologic conditions mimicking it [10]. Bomma et al. [11] showed that less than 30% of patients referred for ARVC actually met the TFC after a comprehensive clinical, invasive and non-invasive re-assessment. The advent of CMR offered a new insight into ARVC [12-18]: due to its superior spatial resolution, unique tissue characterization, increased contrast between

blood pool and endomyocardium and multi-planarity, CMR is considered the gold standard for the assessment of RV volumes and function. The implementation of the new TFC led to a significant reduction in the number of patients confirmed with the diagnosis: Sen-Chowdhry reported an excellent sensitivity but low specificity (29%) of CMR in relation to the TFC [19]. Similar findings were confirmed by Vermes et al. [20,21], which showed a reduction in the prevalence of major and minor CMR criteria after the revised TFC. We found that only 5/124 patients (4%) referred for suspected ARVC actually met the TFC, in keeping with findings from Quarta et al. [22] in a similar cohort. Normal and pathologic conditions mimicking ARVC make the diagnosis even more challenging. Chest wall deformity and non-ARVC related fatty infiltration (obesity, lipomatous metaplasia post-myocardial infarction) could be misinterpreted as ARVC. Moreover, increased RV volumes in athlete's heart or pre-tricuspid shunting often lead to misdiagnosis [24-29]. In our study we observed that 16/124 patients (13%) were found to have ARVC mimics, which were mainly represented by pathologic conditions rather than normal variants mimicking the disease, leading to important clinical implications. In our cohort, the prevalence of ARVC mimics was slightly higher compared with those previously reported in literature: Quarta et al. [22] reported a 5% prevalence of ARVC mimics among patients referred to CMR for suspected ARVC, with similar findings confirmed by Ting et al. [23], which showed a 4.4% prevalence of ARVC mimics. As CMR is part of the multi-modality assessment in patients with suspected ARVC, it is increasingly used in clinical practice, especially due to the potential clinical and prognostic implications that such a diagnosis would carry, and sometimes it is performed to definitely rule out ARVC also in cases where pre-test likelihood is low; we think this might at least in part explain the higher prevalence of ARVC mimics in our cohort. We also assessed the ability of TTE to identify ARVC mimics, and found that CMR was significantly superior (13% by CMR vs 1% by TTE, p=0.01). Although RV volumes were bigger in patients with ARVC and ARVC mimics, as compared to the remaining population, the lack of difference among clinical, ECG, TTE and CMR characteristics between ARVC and ARVC mimics, makes it challenging to identify ARVC mimics in the early differential diagnosis. Interestingly, we also found that 82/124 patients (66%) with suspected ARVC based on clinical assessment showed a structurally normal heart on CMR. Our study confirms and extends previous findings and highlights the limitations of the TFC that do not consider the occurrence of ARVC mimics. Tissue characterization by CMR, including LGE, might help in the differential diagnosis, however, to date, tissue characterization is currently not included among the TFC. The main limitation of our study is the retrospective design; moreover neither endomyocardial biopsy (given its little access in our Centre) nor genetic testing was available in our

cohort. As ARVC is a rare disease, prospective multicentre studies are needed to confirm and expand our findings, aiming at improving the generalizability of our results.

Conclusion:

Out of 2,481 scans performed in our centre over a year, 124 (5%) were performed for suspected ARVC. Based on CMR findings, a pathologic substrate was found in 29% of patients and a structurally normal heart in 66%. ARVC imaging criteria were met in only 4% of patients, while 13% of patients showed findings consistent with ARVC mimics. CMR showed to be superior to TTE in the identification of ARVC mimics (13% vs 1%, p=0.01) and, overall, provided a change in diagnosis in 22% of patients. Accurate identification of the underlying pathology in patients with suspected ARVC is pivotal given the impact on clinical management and prognosis. Our study shows the incremental role of CMR in the identification of ARVC mimics, over and above TTE.

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Table 1. Demographic and clinical characteristics.

Table 2. CMR findings.

Figures captions

Figure 1. Right and left-dominant arrhythmogenic cardiomyopathy.

Top panel. Diastolic (A) and systolic (B) four chamber view showing dilated right ventricle with bulging of the free wall (solid arrows) in a patient meeting one major CMR criterion for ARVC. Bottom panel. Mid-cavity short axis cine sequence (C) with evidence of right ventricular free wall late gadolinium enhancement (LGE) (D, white arrow) and extensive LGE of the interventricular septum (C and D, black arrows) and left ventricular inferolateral wall (D, white pentagon).

Figure 2. Abnormal right ventricular features mimicking ARVC.

Four chamber long axis cine view showing a distorted right ventricle (A) in a patient with pectus excavatum (B, solid white arrow). Four chamber long axis cine view showing heart displacement towards the left with cardiac apex pointing posteriorly (C, white arrow-head) and evidence of lung interposition between the aorta and the pulmonary artery (D, white arrow) in a patient with partial congenital absence of the pericardium.

Figure 3. Pre-tricuspid shunting mimicking ARVC

Four chamber long axis view showing dilated right ventricle (A) in a patient with evidence of atrial septal defect and left to right shunting on the short axis view (B, solid arrow). Four chamber long axis cine view showing dilated right ventricle with septal flattening, in keeping with right ventricular overload (C) in a patient with left upper pulmonary vein (D, white arrow) draining into the brachiocephalic trunk.