Arrythmogenic right ventricular dysplasia/ cardiomyopathy

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Introduction

Arrythmogenic right ventricular dysplasia/cardiomyopathy (ARVD) is a familial cardiomyopathy characterised clinically by right ventricular (RV) dysfunction as well as ventricular tachycardia[1-4] and histopathologically by fibro-fatty replacement of the myocardium.[5] Left ventricular (LV) involvement can occur and appears to correlate with increased disease severity.[3,4] Owing to the complexity of the disease, Task Force Criteria for diagnosis of ARVD were drawn up in 1994 and revised in 2010.[6,7] Cardiovascular magnetic resonance (CMR) findings are now included in the list of major and minor criteria and currently play an important role in establishing the diagnosis of ARVD (see Table I). CMR is extremely valuable for delineation of right ventricular (RV) anatomy and function as well as for characterising the composition of the RV wall, especially regarding the presence of fatty and/or fibrous tissue.

Case report

A 60-year-old woman with metabolic syndrome was referred to us with a history of chest pain, syncopy and palpitations. Her ECG revealed RV strain pattern and inverted T waves in leads V1, V2 and V3. Echocardiographically, her RV wall was thickened and echo-dense and measured 15 mm at the free wall. No definite family history of any specific cardiac abnormality was present. She was referred for a CMR scan to confirm the possible diagnosis of ARVD. The CMR examination was performed with a 1.5-T MR Imager (Philips Medical Systems) using a dedicated cardiac phased array coil. Bright blood cine imaging in the short axis, right ventricular outflow tract (RVOT) and 4 chamber planes were obtained. Black blood images were acquired in short axis and 4 chamber planes with and without fat suppression. Gadolinium was administered at a dose of 1 ml/10 kg (24 ml Omniscan, GE Healthcare) and perfusion sequences performed as well as late enhancement views (LE) in the short axis and 4 chamber planes.

Functional analysis was done utilising the short axis bright blood images. Global decreased contractility of the RV was recorded with the RV ejection fraction measuring 40%.

Diffuse fatty infiltration of the RV wall was clearly visible. The fatty infiltration mainly involved the sub-epicardium of the free wall of the RV (Figs 1-4). Fatty infiltration was also visible in the right atrial free wall as well as the inter-atrial septum (Fig. 5). The LV wall morphology and function was normal. No obvious late enhancement was noted.

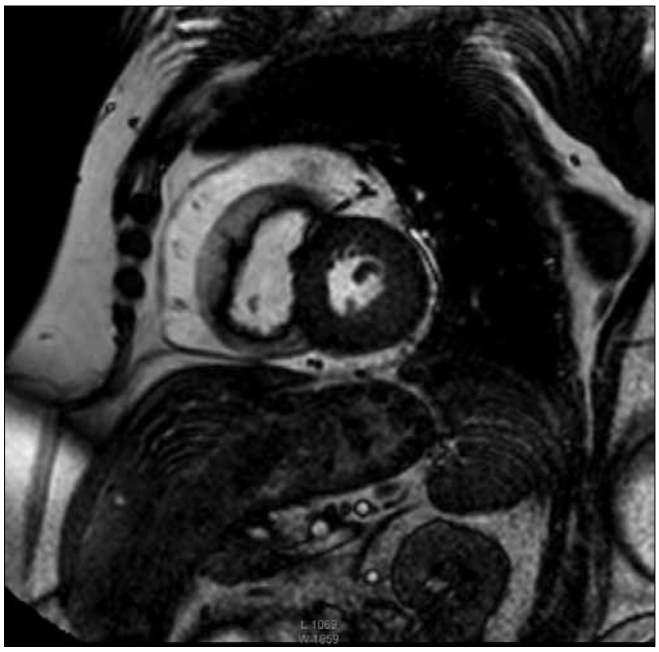

Fig. 1. Short axis bright blood BTFE image. TR=3.4, TE=1.7, Flip=60.

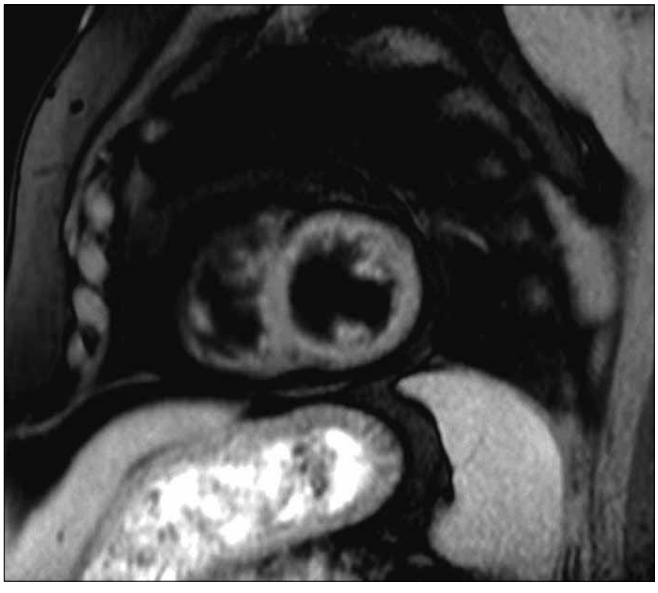

Fig. 2. Short axis dark blood T1 fat sat SPIR TSE TR=612, TE=10.

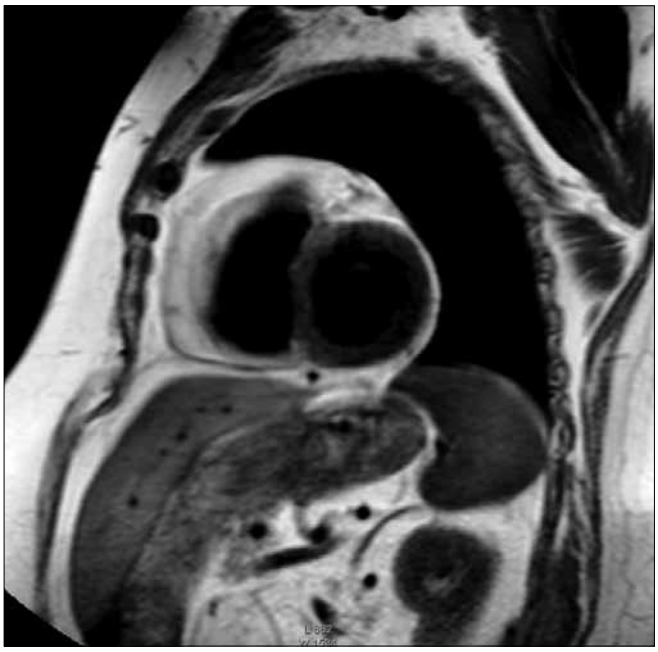

Fig. 3. Short axis dark blood T1 TSE.

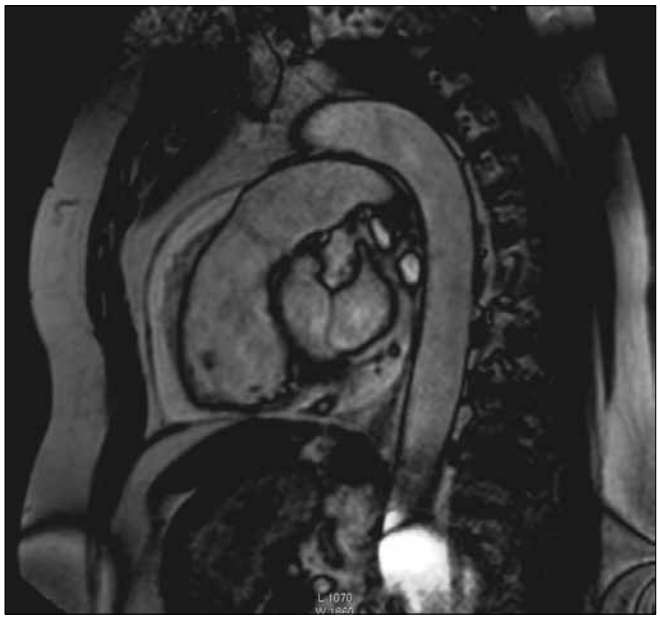

Fig. 4. RVOT bright blood cine BTFE TR=3.4, TE=1.7, Flip=60.

Cardiac catheterisation was undertaken, during which coronary angiography as well as endomyocardial biopsy were performed. Three specimens were taken from the RV free wall. All the coronary vessels appeared normal. Very mild elevated pulmonary arterial pressure was noted (34 mmHg/10 mmHg). Histological investigation revealed the presence of mature fatty tissue as well as fibrous tissue in the RV free wall biopsy specimens. The confirmed presence of fibrous tissue in addition to the marked fatty infiltration on histology suggested the possible diagnosis of ARVD.

Discussion

The term arrhythmogenic right ventricular dysplasia was first used by Frank *et al.* in 1978.[8] Marcus *et al.* were the first to note a familial

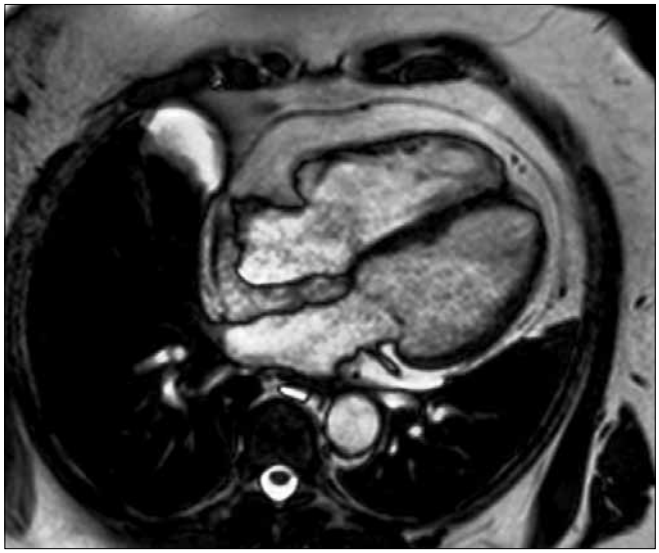

Fig. 5. Four chamber bright blood cine image. BTFE TR=3.4, TE=1.7, Flip=60.

occurrence of ARVD.[1] There are several genetic defects described that lead to an ARVD phenotype, but the exact pathogenesis is still under discussion. Hereditary occurrence in 30% of cases requires the assessment of relatives.

The wide spectrum of clinical presentations includes palpitations, tachy-arrhythmias, cardiac failure and sudden death. The condition is characterised by structural and functional abnormalities of the RV eventually leading to ventricular arrhythmias and progressive RV failure. Ventricular arrhythmias probably occur via the fibromuscular bundles being isolated from each other by fatty tissue, leading to re-entry phenomena. The RV sub-epicardial wall is initially replaced by fibro-fatty tissue often starting in the areas known as the 'triangle of dysplasia',[1] i.e. the inferior tricuspid region, the RV outflow tract and the RV apical region. The fibro-fatty changes eventually progress to involve the whole RV wall trans-murally and globally. Although LV involvement may be found, the LV myocardium is usually spared. Until recently, the only accurate way to confirm the presence of fibro-fatty changes involved endomyocardial biopsy. To lower potential risk, endomyocardial biopsies are usually obtained from the septum region (an area uncommonly affected), so resulting in a lowered sensitivity. (Owing to the marked thickening of the RV wall, the biopsies in our patient could be taken from the free wall, without substantial risk).

The diagnosis of ARVD at its early stages remains a clinical challenge. No single test can be used to establish or exclude ARVD. CMR can assist substantially in the diagnosis of anatomical abnormalities and functional disturbances, as well as detecting the presence of fat or fibrous tissue once they occur.

CMR is superior to 2-D echocardiography in determination of RV mass and volume. CMR allows the acquisition of true short-axis images encompassing the entire RV with high spatial and temporal resolution, so providing highly accurate qualitative RV mass and functional data. Functional abnormalities can be detected on the bright blood cine sequences, and include global or regional hypokinesia resulting in reduced ejection fraction (EF) as well as increased RV volumes.

Table I. Task Force Criteria 2010

Revised Task Force criteria for the diagnosis of ARVC/D[1]
Definite diagnosis: 2 major and 2 minor criteria or 4 minor from different categories
Borderline: 1 major and 1 minor or 3 minor criteria from different categories
Possible: 1 major or 2 minor criteria from different categories

I. Global and/or regional dysfunction and structural alterations*

Major (by 2D echo)
- Regional RV akinesia, dyskinesia, or aneurysm
- *and* one of the following (end diastole):
  - PLAX RVOT≥32 mm (corrected for body size [PLAX/BSA]≥19 mm/m²)
  - PSAX RVOT≥36mm (corrected for body size [PSAX/BSA]≥21 mm/m²
- *or* FAC≤33%

Minor (by 2D echo)
- Regional RV akinesia or dyskinesia
- *and* one of the following (end diastole):
  - PLAX RVOT≥29 to <32 mm (corrected for body size[PLAX/BSA] ≥16 to <19 mm/m²)
  - PSAX RVOT ≥32 to <36mm (corrected for body size [PSAX/BSA]≥18 to <21 mm/m²)
  - *or* FAC>33% to ≤40%

Major (by MRI)
- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
- *and* one of the following:
  - Ratio of RVEDV to BSA (RVEDV/BSA)≥100 ml/m² (female)
  - *or* RVEF ≤40%

Minor (by MRI)
- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
- *and* one of the following:
  - Ratio of RVEDV to BSA (RVEDV/BSA)≥100 to <110 ml/m² (male) or ≥90 to <100 ml/m² (female)
  - *or* RVEF >40% to ≤ 45%

Major (by RV angiography)
- Regional RV akinesia, dyskinesia or aneurysm

II. Tissue characterisation of wall

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

III. Repolarisation abnormalities

Major
- Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 MS)

Minor
- Inverted T waves in leads V1 and V2 in individuals>14 years of age (in the absence of complete RBBB) or in V4, V5, or V6
- Inverted T waves in leads V1, V2, V3 and V4 in individuals >14 years of age in the presence of complete RBBB

IV. Depolarisation/conduction abnormalities

Major
- Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)

Minor
- Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
- Filtered QRS duration (fQRS)≥114 ms
- Duration of terminal QRS <40μV (low-ampplitude signal duration) ≥38ms
- Root-mean-square voltage of terminal 40 ms ≤20μV
- Terminal activation duration of QRS ≥55ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete RBBB

V. Arrythmias

Major
- Nonsustained or sustained VT of LBBB† morphology with superior axis (negative or indeterminate QRS in leads II, III, aVF and positive in lead aVL)

Minor
- Nonsustained or sustained VT or RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and a VF and negative in lead aVL) or of unknown axis
- >500 ventricular extrasystoles per 24 hours (Holter)

VI. Family history

Major
- ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
- ARVD/D confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation‡ categorised as associated or probably associated with ARVC/D in the patient under evaluation

Minor
- History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
- Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative
- ARVD/D confirmed pathologically or by current Task Force Criteria in second-degree relative

*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.
†The orginal document says 'left bundle-branch' or LBB. Dr Frank Marcus has confirmed this should read 'left bundle-branch block' or LBBB.

‡A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

Acronyms

aVF: augmented voltage unipolar left foot lead
aVL: augmented voltage unipolar left arm lead
BSA: body surface area
ECG: electrocardiogram
FAC: fractional area change
LBBB: left bundle-branch block
PLAX: parasternal long axis view
PSAX: parasternal short axis view
RBBB: right bundle-branch block
RV: right ventricular
RVEDV: right ventricular end diastolic volume
RVEF: right ventricular ejection fraction
RVOT: right ventricular outflow tract
SAECG: signal averaged electrocardiogram
VT: ventricular tachycardia

'Modifications of the orginal criteria have been proposed to facilitate clinical diagnosis in first-degree relatives who often have incomplete expression of the disease. According to these recommendations, in the context of proven ARVC/D in a first-degree relative, the diagnosis of familial ARVC/D is based on the documentation of one of the following in a family member:

1. T-wave inversion in right precordial leads V1, V2, and V3 in individuals over the age of 14 years.
2. Late potentials by signal-averaged ECG (SAECG).
3. Ventricular tachycardia of left bundle-branch block morphology on ECG, Holter monitor, or during exercise testing or >200 premature ventricular contractions in 24 hours.
4. Either mild global dilatation or reduction in RV ejection fraction with normal LV or mild segmental dilatation of the RV or regional TV hypokinesis.'[1]

1. Marcus FI, McKenna WJ, Sherrill D, et al. Special report: Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. Circulation 2010;121:1533-1541.

The structural abnormalities occurring in ARVD include RV dilatation (localised or global bulging), right ventricular outflow tract (RVOT) enlargement, thinning of the RV wall (segmental or global) and aneurysm formation.

Fatty infiltration can be detected on the black blood T1-weighted images as well as the cine bright blood images. Fat visualisation on MRI has not been found to be specific for ARVD, however,[9,10] and there is poor inter-reader agreement on reporting of its presence and severity.[11]

Recently, the first observations of delayed enhancement of fibrotic tissue in patients with ARVD have been reported on.[12] Only two-thirds of the patients with ARVD showed delayed enhancement. The reason for the lack of delayed enhancement in the remainder may be the presence of a pure fatty form of ARVD or may simply reflect the insensitivity of current MRI techniques to detect a small amount of fibrosis in early disease. The emergence of techniques enabling us to quantify and refine the detection of localised or diffuse fibrosis will certainly help to improve the sensitivity.[13] Although the presence of fatty or fibrous tissue in the RV wall is not specific, it confirms the diagnosis in the presence of other criteria including a positive family history and specific ECG abnormalities.

Three of the major diagnostic criteria for ARVD according to the new Task Force Criteria were present in our patient, i.e. inverted T waves in V1-V3 on ECG, global hypokinesia of the RV (with increased RV volumes) and histologically proven fibro-fatty changes in the RV wall. The extensive amount of fatty infiltration and thickening of the RV wall in this patient are rare, however, and can possibly be attributed to her additional underlying metabolic abnormality and body habitus (the right atrial wall was also involved, underscoring this). There was a large amount of mediastinal and pericardial fat visible as well. Although all the necessary criteria for the diagnosis of ARVD were present in our patient, her existing metabolic disorder probably contributed to the severity of the fatty infiltration visible in the RV wall.

ARVD remains a difficult disorder to diagnose, but CMR has evolved to become a very valuable adjunctive diagnostic tool.

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