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Impact of new task force criteria in the diagnosis of arrhythmogenic right ventricular cardiomyopathy ☆

Giuseppe Femia [a,1], Chijen Hsu [a,1], Suresh Singarayar [a], Raymond W. Sy [a], Michael Kilborn [a], Geoffrey Parker [b], Mark McGuire [a], Chris Semsarian [a,c,d], Rajesh Puranik [a,*]

[a] Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia
[b] Department of Radiology, Royal Prince Alfred Hospital, Sydney, Australia
[c] Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney, Australia
[d] Sydney Medical School, University of Sydney, Australia

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ABSTRACT

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy that can lead to sudden cardiac death. The diagnostic criterion has recently been revised and through the use of cardiac magnetic resonance (CMR) imaging this study aimed to assess the clinical impact of comparing the original 1994 task force (TF) criterion to the revised 2010 criterion.
Methods: We evaluated 173 consecutive CMR scans of patients referred with clinical suspicion of ARVC between 2008 and 2011. We then compared the prevalence of major and minor CMR criteria by applying the two criteria.
Results: Using the 1994 TF criterion, 13 (7.5%) patients had definite, 11 (6.4%) had borderline, and 39 (22.5%) had possible ARVC. Using the 2010 TF criterion, 10 (5.8%) patients had definite, 1 had borderline, and 7 had (0.04%) possible ARVC. With the 1994 criterion, 81 patients satisfied CMR criterion, of which 36 (44%) had major and 45 (56%) had minor criteria. Upon reclassification with the revised criterion, 61 of the 81 patients were not assigned any criteria, even though many patients had significant risk factors. The negative predictive values (NPV) for both CMR criteria were 100% but the positive predictive values (PPV) for combined CMR major or minor criteria improved from 23% to 55%.
Conclusions: Revision of the criterion has enhanced the diagnostic capabilities of CMR but has resulted in a large cohort of patients not classified. In these patients, there is presently no official consensus on imaging or clinical strategy for surveillance of the evolution of pathology over time.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder that is characterized by myocardial electrical instability and risk for ventricular arrhythmias. Genetic variations are largely found in the desmosomes that are responsible for cell-to-cell binding [1,2], and the mechanical defect of the desmosomes can alter function of the gap junction. ARVC predominantly involves the right ventricle (RV) resulting in progressive loss of myocytes and fibro-fatty infiltration of the RV myocardium, which leads to RV dysfunction and dilatation, and ventricular arrhythmia [3,4]. Apoptosis and necrosis has been demonstrated as a mode of ongoing myocyte death and although not considered an inflammatory cardiomyopathy, ARVC is frequently associated with myocarditis [4]. The regions preferentially involved by this process include the RV inflow tract, the RV outflow tract, and the RV apex; these areas are prone to aneurysmal formation [3]. LV involvement with fibro-fatty replacement, chamber enlargement and myocarditis has been reported in 50–75% of cases but involvement of the inter-ventricular septum is rare [5]. Ventricular arrhythmias arise from the diseased RV and can range from premature ventricular complexes (PVCs) to ventricular tachycardia to ventricular fibrillation; RV outflow tract is the most common site for VT [4].

Structural changes may be very subtle in the early stage of ARVC, and are often confined to a localized region of the RV [4]. During the early stage, patients are often asymptomatic but remain at risk of sudden cardiac death, especially during exertion [5]. As the disease progresses, patients may present with symptomatic arrhythmias, and by this stage RV morphological abnormalities are often discernible by cardiac imaging.

Symptoms of ARVC usually appear between the ages of 30 and 50, but the onset of symptoms can occur from the first decade to the eighth decade of life. The presenting manifestations vary with age and stage of

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* Corresponding author at: Department of Cardiology, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, Sydney, NSW 2050, Australia. Tel.: +61 2 9515 6111; fax: +61 2 9550 6262.
E-mail address: raj.puranik@cmrs.org.au (R. Puranik).
URL: http://www.cmrs.org.au (R. Puranik).

[1] Both authors contributed equally to this work.

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disease [4,6], and they usually consist of palpitations from premature ventricular beats (PVCs), lightheadedness or syncope from rapid monomorphic ventricular tachycardia (VT), or uncommonly sudden death from ventricular fibrillation (VF).

Achieving a definite diagnosis of ARVC is clinically challenging. Even endomyocardial biopsy, often considered to be the gold standard for ARVC, is prone to low sensitivity as sampling is typically taken from the interventricular septum, an area less commonly involved [7]. In 1994, the Task Force (TF) of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology proposed a set of criteria [8], based on medical history, episodes of arrhythmias, ECG changes, morphological, functional, and structural abnormalities. The original TF criterion was based on symptomatic index cases and sudden cardiac death cases, which represented severe phenotypes of disease.

Consequently, these 1994 TF criteria were deemed highly specific, but not sensitive enough for early and familial diseases [4,9]. Of particular concern was that structural and functional criteria were mostly based on qualitative rather than quantitative information, and was mostly developed prior to the increasing experience with more advanced imaging, such as cardiac magnetic resonance (CMR). In 2010 a revised TF criterion was proposed to facilitate clinical diagnosis in first-degree relatives, who often have incomplete or subtle expression of the disease [4,10]. Overall, quantitative criteria were proposed and abnormalities were defined on the basis of comparison with normal subject data [4]. In particular, the revised functional/structural criteria require a combination of regional wall motion abnormalities accompanied by strict volume criteria or ventricular dysfunction.

We investigated the impact of the 2010 TF revisions to the prevalence of ARVC criteria determined by CMR studies in a consecutive series of patients with high degree of clinical suspicion for ARVC.

2. Materials and methods

2.1. Study population

We performed a retrospective analysis of patients referred to our CMR center for suspected ARVC between 2008 and 2011. The majority of referrals came from electrophysiologists based at our institution. All the clinical information, including CMR reports, echocardiogram reports, ECGs, Holter reports, and clinical notes were obtained and analyzed by two experienced cardiologists. In particular, CMR studies were analyzed for the presence or absence of any major and minor criteria using the original 1994 TF criteria and the revised 2010 TF criteria (Table 1). This study was conducted in accordance with the approval given by the Human Research Ethics Committee at our institution (Protocol X11-0341).

2.2. CMR protocol

CMR was performed on a 1.5-T scanner (General Electric HDxt, Milwaukee). ECG-gated steady state free precession cine images were acquired for standard 2- and 4-chamber views, and ventricular outflow tract views in both ventricles (flip angle of 55°, repetition time [TR] = 3.757, echo delay time [TE] = 1.624, field of view 340 × 276). The left ventricle (LV) and RV function were further assessed in a contiguous stack of short-axis slices (slice thickness 10-mm, no gap). Supplementary cine images of the RV were obtained, including transaxial stack views covering the whole of RV from apex to pulmonary valve. A full thoracic late phase MRA was performed to assess anatomy of great vessels and relationship to cardiac structures (slice thickness 3.2 mm, flip angle of 30°, TE = 1.21 ms, TR = 3.58 ms). Delayed enhancement imaging was performed 10 min after injection of 0.2 mmol/kg gadolinium-based contrast agent. A two and three dimensional inversion-recovery segmented gradient echo sequence was used in 2 and 4 chamber, left ventricular outflow tract, right ventricular outflow tract, and short axis views (an in-plane voxel size of 1.3–1.8 × 1.3–1.8 mm^2, slice thickness of 8 mm, flip angle of 20°, TE = 2.98 ms, and TR = 6.44 ms). Velocity mapping of aorta and pulmonary artery were also performed to rule out significant shunt.

Table 1
Definition of major and minor MRI criteria according to the original 1994 TF criteria and the 2010 revised task force criteria.

	Original criteria—1994	Revised criteria—2010
Major criteria	Severe RV dilatation and reduced RVEF (normal LV) or Localized RV aneurysms or Severe segmental RV dilatation	Regional RV akinesia or Regional dyskinesia or Dyssynchronous RV contraction and RVEDVI/BSA ≥ 110 ml/m^2 (male) or RVEDVI/BSA ≥ 100 ml/m^2 (female) or RVEF ≤ 40%
Minor criteria	Mild global RV dilatation and/or reduced RVEF (normal LV) or Regional RV hypokinesia or Mild segmental RV dilatation	Regional RV akinesia or Regional dyskinesia or Dyssynchronous RV contraction and RVEDVI/BSA 100 to 109 ml/m^2 (male) or RVEDVI/BSA 90 to 99 ml/m^2 (female) or RVEF 41% to 45%

LV = left ventricle, RV = right ventricle; RVEDV/BSA = right ventricular end = diastolic volume indexed to body surface area; RVEF = right ventricular ejection fraction; and the Table adapted from Ref. [19].

2.3. Image analysis

All CMR studies were analyzed by 2 experienced readers (SCMR Level III accredited), blinded to the results of other diagnostic tests. Certified CMR evaluation software (OsiriX v.3.9.3, Pixmeo, Switzerland) was used for viewing and analysis. The endocardial LV and RV contours were hand-drawn for each diastolic and systolic frame.

2.4. Statistical analysis

Those data with continuous parameters are expressed as mean ± standard deviation (SD). TF criteria were expressed as dichotomous data. Any differences between groups were assessed by the McNemar test, and P value < 0.05 was considered significant.

3. Results

3.1. Demographics

A total of 173 consecutive CMR scans of patients with clinical suspicion of ARVC were identified between 2008 and 2011; patient characteristics are listed in Table 2. The most common reasons for the CMR referral were documented VT/VF (46.9%), and family history of sudden cardiac death or ARVC (22.8%). Of the 173 CMR scans performed, 91 (53%) CMR scans were found to be normal, and 81 (47%) scans were abnormal. Unexpected cardiac and extra-cardiac abnormalities are listed in Table 3, and included extra-cardiac masses, detection of left ventricular scar, and anomalous pulmonary venous drainage.

3.2. Diagnosis of ARVC and followup

Using the original 1994 TF criterion, which took into account family history, ECG, ventricular arrhythmias, and tissue characteristics; 13 (7.5%) patients satisfied the criteria for definite ARVC, 11 (6.4%) for borderline ARVC, and 39 (22.5%) for possible ARVC. Using the revised 2010 TF criterion, 10 (5.8%) patients satisfied the criteria for definite ARVC, 1 patient for borderline ARVC, and 7 (0.04%) patients for possible ARVC (Fig. 1).

It should be noted that five of the 10 patients diagnosed with definite ARVC satisfied the definite ARVC criteria without counting imaging (functional/structural) criteria, having satisfied other non-imaging based categories of criteria. Regardless of whether 2010 revised imaging (function/structure) criterion was utilized to contribute to the diagnosis

Table 2
Patient characteristics.

Variables	Patients (n = 173)
Age, years	43 +/− 17
Male, sex, n (%)	106 (60.5%)
Indications, n (%)	
Family history sudden cardiac death or ARVC	40 (22.8%)
Cardiac arrest	8 (4.5%)
VT/VF	82 (46.9%)
Arrhythmias (non-VT/VF)	21 (12.0%)
Echocardiogram abnormality	6 (3.4%)
Abnormal ECG	18 (10.2%)
RVEF (%)	52.6 +/− 6.9
RVEDV/BSA, ml/m2	100.2 +/− 24.8

ARVC = arrhythmogenic right ventricular cardiomyopathy/dysplasia; VT = ventricular tachycardia; and VF = ventricular fibrillation