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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Clinical Diagnosis, Imaging, and Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

JACC State-of-the-Art Review

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy that can lead to sudden cardiac death and heart failure. Our understanding of its pathophysiology and clinical expressivity is continuously evolving. The diagnosis of ARVC/D remains particularly challenging due to the absence of specific unique diagnostic criteria, its variable expressivity, and incomplete penetrance. Advances in genetics have enlarged the clinical spectrum of the disease, highlighting possible phenotypes that overlap with arrhythmogenic dilated cardiomyopathy and channelopathies. The principal challenges for ARVC/D diagnosis include the following: earlier detection of the disease, particularly in cases of focal right ventricular involvement; differential diagnosis from other arrhythmogenic diseases affecting the right ventricle; and the development of new objective electrocardiographic and imaging criteria for diagnosis. This review provides an update on the diagnosis of ARVC/D, focusing on the contribution of emerging imaging techniques, such as echocardiogram/magnetic resonance imaging strain measurements or computed tomography scanning, new electrocardiographic parameters, and high-throughput sequencing. (J Am Coll Cardiol 2018;72:784–804)

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) was recognized as a specific entity in the 1970s by our group when several patients with drug-resistant right ventricular (RV) tachycardia had surgery guided by epicardial mapping. Interventions provided evidence of their RV origin, with RV dilatation, late potentials, left-sided extension, and fibrofatty infiltration in RV biopsy specimens (1). Guy Fontaine coined the term dysplasia, appropriate for this condition, and published the first large series in 1982 with Frank Marcus, including 22 severe cases with RV arrhythmia, 12 of which needed surgery (2). All had local or global RV enlargement and showed electrocardiography (ECG) abnormalities with T-wave inversions in the RV precordial leads from V_1 to V_4 and late potentials, either obvious by ECG (called epsilon waves) or signal-averaged ECG.

ARVC/D has been included in the classification of the European group for cardiomyopathies since 1994. The denomination of this cardiomyopathy has been discussed for years. The "ARVC" and "ARVD"

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terminology represents 2 different visions of its pathophysiology: degenerative process or development abnormality. Although the terminology of "dysplasia" is probably questionable, this term has been used and accepted for 40 years. Several combined diagnostic criteria (task force criteria [TFC]) were proposed, classified as major or minor (3), and implemented in 2010 (4) (**Table 1**) for a better specificity, particularly in family members and young athletes. The diagnosis of ARVC/D is probably the most challenging in the field of inherited cardiomyopathies because of the absence of specific unique diagnostic criteria, its variable expressivity, and its incomplete penetrance in relatives. The main problem is that a definitive pathological diagnosis is only given by a seldom available histological study obtained by biopsy, surgery, or necropsy. Indirect evidence can be obtained by multimodal cardiac imaging studies. ECG data show RV disease, but other RV cardiomyopathies may alter it in a similar way, such as myocarditis (5), which interacts with ARVC/D (6,7), sarcoidosis (8,9), or the rare Uhl's disease (**Table 2**).

The revision of ARVC/D diagnostic criteria in 2010 increased the specificity of the diagnosis, but it still lacks sensitivity, especially in the early stages of the disease (4,10). In addition, most diagnostic criteria were assessed relative to healthy controls and possibly lack specificity for differential diagnosis with other arrhythmogenic diseases involving the right ventricle. Genotype/phenotype studies have shown that ARVC/D, which was initially described as an isolated or predominant RV disease, exhibits frequent left ventricular (LV) involvement. This involvement may be present or predominant at early stages in some mutation carriers, expanding the clinical spectrum of the disease to a larger group of scar-related cardiomyopathies or arrhythmic cardiomyopathies according to the suggestion of some authors.

The present review provides an update on the pathological, clinical, and genetic abnormalities associated with ARVC/D, focusing on the contribution of emerging imaging techniques and genetics for diagnosis.

PATHOLOGY

The main anatomopathological feature of ARVC/D is the replacement of myocytes by fibrous or fibro-adipose tissue in the RV free wall. Lesions extend from the epicardium to the endocardium and predominantly involve the area between the anterior part of the pulmonary infundibulum, the apex, and the infero-posterior wall (the so-called "triangle of dysplasia"). Myocyte loss and fibrous replacement are most often segmental and usually do not involve the interventricular septum. LV histological involvement is frequently reported in autopsy cases or explanted hearts, even in the absence of macroscopic LV involvement (11).

Various histological forms have been described depending on the predominance of fibrous or adipose tissue. Nevertheless, a systematic study of myocardial biopsy specimens revealed the absence of specific RV fat infiltration in contrast to extensive fibrous tissue and myocyte loss (12). Fatty infiltration is thus not required as a histological diagnostic criterion (4). Lymphocytic or histiocytic inflammatory infiltrates, focal necrosis, and signs of apoptosis are frequent (13). The association of ARVC/D with clinical and histological features of myocarditis is thus not rare, underlying the relation between the 2 diseases (7). However, the role of viruses in ARVC/D pathogenesis remains unknown (14,15). A decrease in desmosomal protein staining (e.g., plakoglobin, desmosomal cadherins) has been reported in immunostaining studies, but the reproducibility and the diagnostic accuracy of these techniques in routine practice were not assessed (16,17). Fibrofatty replacement is not specific to desmosomal ARVC/D, as a similar pattern was found in *TMEM*-43, *PLN*, and *LMNA*-related "ARVC/D" (18–20), as well as arrhythmogenic mitochondrial cardiomyopathy associated with *PPA2* mutations and arrhythmogenic dilated cardiomyopathy (DCM) caused by *FLNC* mutations (21,22).

The diagnostic yield of endomyocardial biopsies is relatively low and largely depends on the location and number of targeted sites because of the patchy nature of fibrous replacement and the subepicardial location of lesions. Endomyocardial biopsies are generally noncontributive on the right side of the interventricular septum. Voltage-guided endomyocardial biopsy probably increases the diagnostic yield, but questions remain on the safety of performing biopsies on the RV free wall (12,23). However, voltage-guided biopsies may be useful in ruling out some differential diagnoses, such as sarcoidosis or viral myocarditis (5,8).

ELECTROCARDIOGRAM

ECG DIAGNOSTIC CRITERIA. The search for ARVC/D is initiated in 2 clinical situations. For patients with ventricular arrhythmia, mainly of RV origin on the ECG, the diagnosis is approached through RV

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

4D = 4-dimensional

ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia

CT = computed tomography

DCM = dilated cardiomyopathy

ECG = electrocardiography

LBBB = left bundle branch block

LGE = late gadolinium enhancement

LV = left ventricular

MDCT = multidetector computed tomography

MRI = magnetic resonance imaging

RBBB = right bundle branch block

RV = right ventricular

RVOT = right ventricular outflow tract

SCD = sudden cardiac death

SSFP = steady-state free precession

TFC = task force criteria