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Review

Current and state of the art on the electrophysiologic characteristics and catheter ablation of arrhythmogenic right ventricular dysplasia/cardiomyopathy

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ABSTRACT

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited genetic disease caused by defective desmosomal proteins, and it has typical histopathological features characterized by predominantly progressive fibro-fatty infiltration of the right ventricle. Clinical presentations of ARVD/C vary from syncope, progressive heart failure (HF), ventricular tachyarrhythmias, and sudden cardiac death (SCD). The 2010 modified Task Force criteria were established to facilitate the recognition and diagnosis of ARVD/C. An implantable cardiac defibrillator (ICD) remains to be the cornerstone in prevention of SCD in patients fulfilling the diagnosis of definite ARVD/C, especially among ARVD/C patients with syncope, hemodynamically unstable ventricular tachycardia (VT), ventricular fibrillation, and aborted SCD. Further risk stratification is clinically valuable in the management of patients with borderline or possible ARVD/C and mutation carriers of family members. However, given the entity of heterogeneous penetrance and non-uniform phenotypes, the standardization of clinical practice guidelines for at-risk individuals will be the next frontier to breakthrough.

Antiarrhythmic drugs are prescribed frequently to patients experiencing frequent ventricular tachyarrhythmias and/or appropriate ICD shocks. Amiodarone is the recommended drug of choice. Radiofrequency catheter ablation (RFCA) has been demonstrated to effectively eliminate the drug-refractory VT in patients with ARVD/C. However, the efficacy and clinical prognosis of RFCA via endocardial approach alone was disappointing prior to the era of epicardial approach. In recent years, it has been proven that the integration of endocardial and epicardial ablation by targeting the critical isthmus or eliminating abnormal electrograms within the diseased substrates could yield higher acute success and lower recurrence of ventricular tachyarrhythmias during long-term follow-up. Heart transplantation is the final option for patients with extensive disease, biventricular HF with uncontrollable hemodynamic compromise, and refractory ventricular tachyarrhythmias despite aggressive medical and ablation therapies.

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Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy, which was first described in 1965 [1]. ARVD/C predominantly affects the right ventricle (RV) with fibrofatty replacement pathologically. The left ventricle (LV) involvement, typically the posterior lateral wall, accounts for an estimated 10% of patients, and presents usually as one of the late manifestations [2,3]. Mutations of seven dominant genes in the desmosome result in defective cell-to-cell binding and contribute to the pathogenesis of ARVD/C.

The presentations of ARVD/C are diverse, ranging from syncope, heart failure (HF), and sudden cardiac death (SCD). The clinical courses have been categorized into four phases: concealed phase, overt electrical disorder, RV failure, and bi-ventricular failure [3]. Overlapping of each phase may occur. Given the diversity of disease course, the 2010 modified Task Force (TF) criteria were proposed to facilitate the diagnosis [4]. Nevertheless, risk stratification for individuals with ARVD/C and at-risk subjects is of clinical significance. In this review, we summarize current diagnostic guidelines, risk stratification schemes, and the management of ARVD/C.

Diagnosis of ARVD/C: from past to present

McKenna et al. [5] initially proposed international TF criteria for the diagnosis of ARVD/C in 1994, and Marcus et al. [4] revised them (Fig. 1) through the incorporation of new knowledge and technology to improve the diagnostic sensitivity and yet to maintain diagnostic specificity. Quantitative parameters, particularly imaging studies, were used. Individuals are categorized into definite, borderline, or possible diagnosis of ARVD/C after detailed investigation of structural, histological, electrocardiographic, arrhythmogenic, family history, and genetic features of the disease. The modification of the TF criteria maintains the major and minor criteria for each aspect to facilitate clinical diagnosis of ARVD/C in early stage and first-degree relatives with incomplete expression of the disease [6].

Based on the revised TF criteria, series of evaluations consisting of non-invasive studies of electrocardiography (ECG), signal averaged ECG, echocardiogram and/or magnetic resonance imaging (MRI), Holter monitoring, genetic analysis, and invasive studies of RV angiography, RV endomyocardial biopsy (EMB), are recommended for individuals at-risk to establish the diagnosis. Importantly, although 12-lead ECG (Fig. 2) is considered as an initial screening tool, 12% of patients with ARVD/C may have normal ECG [7], emphasizing the need for comprehensive clinical evaluations.

Structural abnormalities in ARVD/C can be evaluated by echocardiogram, MRI noninvasively, or RV angiography invasively. Incorporation of quantitative parameters by echocardiography or MRI yields high specificity (90–98% for major criteria) [4]. However, the application of revised TF criteria significantly reduced the incidence of structural abnormalities fulfilling any diagnostic criteria than the original criteria [8]. On the other hand, despite the development of computerized analysis in quantifying RV abnormalities by angiography [9,10], the presence of RV akinesia, dyskinesia, or aneurysm remains one of the major criteria. RV angiography may depict sacculation, segmental contraction impairment, and variable trabecular patterns in patients with ARVD/C [11], and therefore, remains the gold standard for structural assessment in some laboratories.

Distinguishing ARVD/C from other mimicking diagnoses, such as idiopathic RV outflow tract tachycardia (RVOT VT), myocarditis, sarcoidosis, or endomyocardial fibrosis, is warranted. Assessment of transmural fibrofatty infiltration by means of EMB may provide valuable histopathological features despite potential risk of free wall perforation and possibility of false negative results owing to the nature of segmental involvement. Guiding EMB based on the low voltage area identifiable on electroanatomic mapping (EAM) may yield higher diagnostic sensitivity [12].

Of note, electrophysiological studies by programmed stimulation (PVS) not only have a pivotal role in evaluating the vulnerability of ventricular tachyarrhythmias, but provide clues for the diagnosis of ARVD/C. Denis et al. [13] demonstrated that either the presence of polymorphic premature ventricular contractions (PVCs) with $\geq$1 couplet or sustained or nonsustained VT with left bundle branch block (LBBB) after excluding RVOT VT by high dose isoproterenol (45 μg/min) infusion could help in making the diagnosis of ARVD/C in the early stage of disease yielding a sensitivity of 91.4% and a specificity of 88.9%.

Risk stratification and disease progression of ARVD/C

Risk stratification in patients with ARVD/C

Several factors have been proposed [2,14–16] for stratifying the risk of mortality and/or ventricular tachyarrhythmias in ARVD/C. Corrado et al. [17] established an arrhythmic risk stratification pyramid, which categorized patients with ARVD/C into highest, intermediate, and lowest risk groups according to the variables shown in Fig. 3A to facilitate early recognition of individuals who would be benefit from an implantable cardioverter-defibrillator (ICD) implantation. Because of a high annual arrhythmic risk up to 8–10%, an ICD implantation is mandatory for those with aborted SCD, hemodynamically unstable sustained VT, or syncope.