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REVIEW

Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy: Progress and Pitfalls

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy that predominantly affects the right ventricle. With a prevalence in the range of 1:5000 to 1:2000 persons, ARVC is one of the leading causes of sudden cardiac death in young people and in athletes. Although early detection and treatment is important, the diagnosis of ARVC remains challenging. There is no single pathognomonic diagnostic finding in ARVC; rather, current international task force criteria specify diagnostic major and minor criteria in six categories: right ventricular imaging (including echocardiography and cardiac magnetic resonance imaging (MRI)), histology, repolarisation abnormalities, depolarisation and conduction abnormalities, arrhythmias and family history (including genetic testing). Combining findings from differing diagnostic modalities can establish a ''definite'', ''borderline'' or ''possible'' diagnosis of ARVC. However, there are limitations inherent in the current task force criteria, including the lack of specificity for ARVC; future iterations may be improved, for example, by enhanced imaging protocols able to detect subtle changes in the structure and function of the right ventricle, incorporation of electro-anatomical data, response to adrenergic challenge, and validated criteria for interpreting genetic variants.

Keywords Arrhythmogenic ventricular cardiomyopathy • Diagnosis • Criteria

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) was first reported in 1982 [1] and is an inherited cardiomyopathy that predominantly affects the right ventricle. Recent reports suggest using the term ''arrhythmogenic cardiomyopathy'', since the condition can also exhibit biventricular involvement. It is one of the leading causes of sudden cardiac death in young people and athletes [2,3]. This article reviews the current diagnostic criteria for ARVC and highlights clinically challenging areas of difficulty and emerging concepts.

Pathology

The distinctive histopathological feature of ARVC is the replacement of normal right ventricular myocardial tissue with fibrofatty tissue. The process progresses from the epicardium toward the endocardium and results in wall thinning and aneurysmal dilatation. This is typically localised in the so-called ''triangle of dysplasia'' which is constituted by the inflow tract, outflow tract and apex of the right ventricle. The genetic basis of disease primarily involves defects in the cardiac desmosomes. These proteins are important in cell-to-cell adhesion and they are also

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important mediators of intracellular and intercellular signal transduction.

Epidemiology

The prevalence of ARVC is estimated in the range of 1:5000 to 1:2000 persons. Approximately 50% of patients have a positive family history. The disease is typically transmitted with an autosomal dominant pattern of inheritance. Both incomplete penetrance and limited phenotypic expression are common. ARVC is more malignant in men than in women. Participants undertaking strenuous exercise or competitive sports are also more frequently affected, probably due to mechanical stress which exaggerates phenotypic expression of desmosomal dysfunction [4,5].

Clinical Presentation and Natural History

Arrhythmogenic right ventricular cardiomyopathy typically becomes clinically apparent between the second and fourth decades of life [4,6]. Clinically, overt disease is preceded by a preclinical phase which is characterised by minimal or no structural abnormalities. Sudden death may be the first clinical manifestation of the disease, with recent evidence suggesting sudden cardiac death may occur in gene carriers with no phenotypic evidence of disease, the so-called concealed phase [3].

The most common clinical presentation is palpitations or effort-induced syncope in young adults with the electrocardiograph (ECG) showing T-wave inversion in the right precordial leads, ventricular arrhythmias with a left bundle-branch block pattern and right ventricular abnormalities on imaging tests. Electrocardiographic depolarisation abnormalities that reflect abnormal conduction through the diseased right ventricular myocardium, can also be present. Diagnostic findings on imaging studies consist of global dilatation and dysfunction and regional wall-motion abnormalities, predominantly affecting the right ventricle. End-stage right ventricular or biventricular pump failure may develop in patients with long-standing disease.

Diagnosis

There is no single diagnostic finding that is pathognomonic of ARVC. In 1994 an international task force proposed a diagnostic scoring system with major and minor criteria to standardise the clinical diagnosis of ARVC [7]. These criteria were highly specific but lacked sensitivity for the diagnosis of early forms of the disease [8]. The criteria were revised in 2010 to incorporate new findings and diagnostic modalities to improve the sensitivity while preserving specificity [9,10]. The main modifications were the introduction of precise quantitative measurements to the imaging criteria, the addition of new electrical parameters and the expansion of the family history criteria to include genetic analysis (see Table 1, 2010 task force criteria).

The current task force criteria combine diagnostic criteria from six categories. The criteria are classified as major and minor criteria. For the evaluation for ARVC, different diagnostic modalities must be combined and these findings then establish ''definite'', ''borderline'' or ''possible'' diagnosis of ARVC. Definite ARVC diagnosis includes two major criteria, or one major and two minor criteria, or four minor criteria from different categories. Borderline ARVC includes one major and one minor criteria, or three minor criteria from different categories. Possible ARVC includes one major or two minor criteria from different categories.

Echocardiography

Echocardiography is currently the first-line imaging modality for the diagnosis of ARVC in many centres. The 2010 task force criteria include echocardiographic evaluation of RV akinesia, dyskinesia or aneurysms together with measurements of right ventricular outflow tract (RVOT) diameter and right ventricular (RV) fractional area change. However, diagnosing ARVC by echocardiography is challenging. In particular, quantitative assessment of RV function is difficult due to its complex anatomy and load dependency. Discrepancy between findings on echocardiography and cardiac magnetic resonance imaging (MRI) has been observed with a recent study showing that only 50% of patients satisfying CMR criteria for ARVC also fulfilled the 2010 echocardiographic criteria [11].

Cardiac MRI

For cardiac MRI, the task force criteria include assessment of regional RV akinesia, dyskinesia or dyssynchronous RV contraction together with volumetric measurements or a decreased RV ejection fraction. Compared to echocardiography, cardiac magnetic resonance (CMR) provides more accurate and reproducible measurements of chamber dimensions, volumes and function [12] (see example in Figure 1). In addition, it can provide non-invasive tissue characterisation with the use of late gadolinium enhancement (LGE). This provides information about the presence and amount of fibrofatty myocardial scarring and may help to distinguish ARVC from other cardiomyopathies [13]. These advantages make CMR the preferred imaging modality for the diagnosis of ARVC. However, it is notable that LGE has not been incorporated into the current task force criteria. Although LGE can be detected in the RV and left ventricle (LV) in up to 88% and 61% of ARVC patients respectively, LGE detection can be difficult in the thin-walled right ventricle and differentiation between fat and fibrosis can be challenging [14].

T1 mapping is a novel technique in cardiac MRI that can quantify native T1 relaxation time of the myocardium and depict it in a colour-encoded T1 map. With the use of T1 mapping, it is possible to detect even relatively small diffuse myocardial abnormalities. By quantifying tissue characteristics through T1 mapping it also becomes feasible to follow longitudinal changes. Hence, T1 mapping seems promising

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