Diagnostic Criteria, Genetics, and Molecular Basis of Arrhythmogenic Cardiomyopathy

Cristina Basso, MD, PhD*, Kalliopi Pilichou, PhD, Barbara Bauce, MD, PhD, Domenico Corrado, MD, PhD, Gaetano Thiene, MD

KEYWORDS

• Arrhythmogenic right ventricular cardiomyopathy • Desmosomes • Sudden cardiac death • Implantable cardioverter defibrillator

KEY POINTS

- Clinical presentation is characterized by ventricular arrhythmias at risk of sudden death. More rarely, right ventricular or biventricular dysfunction leading to heart failure is reported
- Generally referred as right ventricular disease, recognition of left-dominant and biventricular subtypes prompted the use of the broader term AC.
- Effort is a trigger of disease onset and progression as well as ventricular arrhythmias.
- Disease causing genes mostly encode for desmosomal proteins, although non-desmosomal genes are also described.
- Knowledge of phenocopies that can mimic AC is essential to avoid misdiagnosis.

Arrhythmogenic cardiomyopathy (AC) is an inherited, genetically determined heart muscle disease characterized by myocardial atrophy with fibrofatty repair. It usually manifests with electrocardiographic (ECG) abnormalities, syncope, or ventricular arrhythmias during adolescence or young adulthood.[1–5] AC represents one of the major causes of sudden death in the young and athletes.[1,6] The disease is listed among rare cardiovascular disorders, because its estimated prevalence in the general population ranges from 1:2000 to 1:5000.[7,8]

The structural substrate of AC consists of myocardial atrophy, which occurs progressively with time, through periodic "acute bursts" of an otherwise stable disease, starting from the epicardium and eventually extending down to reach the endocardium to become transmural ("wave-front phenomenon"). Myocyte necrosis is seldom evident, as a proof of the acquired and progressive nature of myocardial atrophy. Myocardial inflammation has been reported in up to 75% of autoptic AC hearts and probably plays a role in triggering life-threatening ventricular tachyarrhythmias.

Right ventricular (RV) aneurysms, whether single or multiple, located in the so-called triangle of dysplasia (ie, inflow, apex, and outflow tract), are pathognomonic features of AC, although not always present.[1,2] Nevertheless, apparently normal hearts have been reported in which only a careful histopathology investigation can reveal fibrofatty

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Department of Cardiac, Thoracic, and Vascular Sciences, University of Padova Medical School, Padova, Italy
* Corresponding author. Department of Cardiac Thoracic and Vascular Sciences, University of Padua Medical School, Via Gabelli, Padova 61-35121, Italy.
E-mail address: cristina.basso@unipd.it

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replacement, in the absence of wall thinning, aneurysm, and chamber dilatation. Cases with isolated or predominant left ventricular (LV) involvement are increasingly detected.

Genetic studies have led to the identification of more than 10 disease-causative genes associated with AC. Nearly half of AC patients harbor mutations in genes encoding desmosomal proteins and less than 1% in non–desmosomal genes.[7]

With the gradual understanding of the genetic basis of the disease, the original name "dysplasia" was no longer considered proper and the term "cardiomyopathy" was introduced.[1–5,8] Moreover, because similar pathologic changes and arrhythmic manifestations may also occur in the setting of predominant involvement of the left ventricle,[9] the preferred disease name is now simply AC.

CLINICAL FEATURES

Clinical manifestations vary with age and disease stage. Despite the similar prevalence of mutation carriers in both genders, the clinical expression of the disease is usually more severe in men, with a higher prevalence of male than female patients who fulfill the diagnostic criteria (up to 3:1).[3,5] Palpitations, syncope, and cardiac arrest are common symptoms in young adults or adolescents, and the most typical signs of AC are ventricular arrhythmias with left bundle branch block (LBBB) morphology (either premature ventricular complexes or ventricular tachycardia [VT]) and T-wave inversion in precordial leads in the 12-lead ECG. Less common are RV and biventricular dilatation, with or without heart failure, mimicking dilated cardiomyopathy and requiring heart transplantation at the end stage.

Not infrequently, the patient can present with a myocarditis or a myocardial infarction-like picture with chest pain, dynamic ST-T wave changes on the 12-lead ECG, and myocardial enzyme release in the setting of normal coronary arteries.[3]

Traditionally, 4 clinical phases have been described in the classic RV variant of AC and include the following: (a) a concealed phase, with subtle RV structural changes, with or without ventricular arrhythmias, during which sudden death may even be the first manifestation of the disease; (b) an overt electrical phase, with symptomatic life-threatening ventricular arrhythmias associated with clear-cut RV morphofunctional abnormalities; (c) RV failure, due to progression and extension of the RV disease; and (d) biventricular failure, caused by advanced LV disease.[10] Sudden death due to electrical instability can occur at any time during the course of the disease.[3,5,6,11,12] The incidence of sudden death ranges from 0.08% to 3.6% per year in adults with AC.[3,5,11]

Although scar-related reentry VT is the most frequent event in patients with an overt phenotype, ventricular fibrillation (VF) can occur in patients with an early stage or "hot phase" of the disease because of acute myocyte death and inflammation.[11,12] A possible role of gap junction remodeling with sodium channel interference has been also advanced to account for life-threatening arrhythmias.[13,14]

DIAGNOSTIC CRITERIA

Because there is no single gold standard, AC diagnosis requires multiple criteria, combining different sources of diagnostic information, such as morphofunctional (by echocardiography and/or angiography and/or cardiac magnetic resonance [CMR]), histopathological on endomyocardial biopsy, ECG, arrhythmias, and familial history, including genetics (**Fig. 1**).

The original diagnostic criteria[15] were revised in 2010[16] to improve diagnostic sensitivity, by maintaining diagnostic specificity (**Box 1**). Quantitative parameters have been included and abnormalities defined, based on the comparison with normal subject data. Moreover, T-wave inversion in V_1-V_3, and VT with a LBBB morphology with superior or indeterminate QRS axis (either sustained or no sustained), have become major diagnostic criteria[17]; T-wave inversion in V_1-V_2 in the absence of right bundle branch block (RBBB), and in V_1-V_4, in the presence of complete RBBB, has been included among the minor criteria (**Fig. 2**). Finally, major criteria in the family history category include the confirmation of AC in a first-degree relative, either by fulfilling the criteria or pathologically (at autopsy or transplantation), and the identification of a pathogenic mutation, categorized as associated or probably associated with AC. However, caution is recommended because the pathogenic significance of a single mutation is increasingly questioned, particularly in the era of next generation sequencing (NGS).

The diagnostic criteria are also valid in the pediatric age group, with the only exception of inverted T wave in right precordial leads in children less than 12 years of age, which is often normal. Noteworthy, AC diagnosis is exceptionally made younger than the age of 10 because of the age-related penetrance of the disease.[3,5]

After 2010, the exploding use of contrast-enhanced CMR in the routine clinical workup increasingly revealed left dominant variants of AC that escape clinical identification through current diagnostic criteria, thus underlying their limitations