Arrhythmogenic Cardiomyopathy
Advances in Diagnosis and Disease Pathogenesis

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Arrhythmogenic cardiomyopathy is the most arrhythmogenic form of human heart disease and a major cause of sudden death in the young.1,2 Originally described as a right ventricular disease (arrhythmogenic right ventricular cardiomyopathy),3 it is now recognized to include a spectrum of biventricular and left-dominant forms that may be misdiagnosed as dilated cardiomyopathy or myocarditis.4–7 Arrhythmias occur early in the natural history of arrhythmogenic cardiomyopathy, often preceding structural remodeling of the myocardium.1,8 Thus, in its early manifestations, arrhythmogenic cardiomyopathy is more reminiscent of the ion channelopathies than other forms of nonischemic cardiomyopathy.

Arrhythmogenic cardiomyopathy has been linked to mutations in genes encoding desmosomal proteins (PKP2, DSG2, DSC2, DSP, and JUP).9,10 Desmosomes, cell-cell adhesion organelles, are especially abundant in heart and skin, tissues that normally experience mechanical stress.1,11 Therefore, it is not surprising that clinical phenotypes in patients with desmosomal mutations take the form of myocardial and cutaneous diseases. Indeed, patients with arrhythmogenic cardiomyopathy are particularly prone to disease exacerbations in response to strenuous exercise, emphasizing the importance of biomechanical determinants of disease. However, compared with other familial cardiomyopathies and ion channelopathies associated with sudden death, arrhythmogenic cardiomyopathy has low penetrance and unusually variable disease expression, even within members of the same family who carry the same disease-associated mutation.8–10 This indicates the presence of powerful genetic and/or epigenetic modifiers that interact with environmental factors such as exercise to determine the risk of sudden death or other adverse events. It also helps explain why diagnosis and risk stratification can be so challenging.

In 1994, an International Task Force proposed criteria for the diagnosis of arrhythmogenic cardiomyopathy.12 In practice, these criteria were found to be highly specific but not very sensitive, especially in detecting early disease or identifying affected relatives of probands. These criteria were updated in 2010 to incorporate the significant progress made in understanding the pathobiology of arrhythmogenic cardiomyopathy and thereby improve diagnostic yield.13 This brief review focuses on recent progress in diagnosis and disease pathogenesis.

Understanding the Genetic Basis of Arrhythmogenic Cardiomyopathy

Long before the discovery of disease alleles, the original 1994 diagnostic criteria recognized the familial nature of arrhythmogenic cardiomyopathy.12 Confirmation of familial disease at autopsy or surgery was considered a major diagnostic criterion, and a family history of premature sudden death (<35 years) resulting from suspected arrhythmogenic right ventricular cardiomyopathy and family history of clinically documented arrhythmogenic right ventricular cardiomyopathy were minor criteria. The revised 2010 criteria now include identification of a pathogenic mutation as a major criterion.13 However, despite remarkable advances in our understanding of the genetic basis of arrhythmogenic cardiomyopathy, the role of genetic testing in diagnosis and management remains uncertain.

It appears that the revised criteria can better identify individuals who carry disease-causing mutations in 1 or more desmosomal protein genes. For example, in studies reported shortly before the new criteria were published, desmosomal gene mutations were identified in ∼50% of individuals who fulfilled the original 1994 criteria, but in a much smaller number of family members or individuals with suspected disease who did not meet the criteria.14,15 In a follow-up study of a Dutch cohort evaluated by the 2010 criteria, pathogenic desmosomal mutations were found in 87 of 149 index cases (58%).16 Disease was diagnosed by the new criteria in 60 of 302 family members (18 symptomatic, 42 asymptomatic), of whom 90% carried pathogenic mutations.16 Another recent study assessed the role of genotyping in 210 first-degree and 45 second-degree relatives in 100 families in which probands fulfilled the 2010 criteria (in 51 families, the proband was deceased).17 Disease-causing mutations were identified in 58% of families and 73% of living probands, who generally had more severe disease than relatives. Of 93 relatives with a causal mutation, 33% fulfilled the 2010 criteria, but only 19% met the 1994 criteria. Interestingly, 28% of living probands and 10% of relatives had an additional sequence variant in a desmosomal gene that, in relatives, was associated with a 5-fold greater risk of developing penetrant disease. This finding adds to a growing body of evidence that disease expression and severity may be determined by the presence of multiple mutations or a combination of disease alleles and 1 or more sequence variants that, by themselves, are insufficient to cause disease.8–10,18

Clearly, genetic screening based on sequencing only a few candidate genes is inadequate for either diagnosis or risk
stratification. The same is undoubtedly true in hypertrophic cardiomyopathy and the ion channelopathies, but the potential effects of genetic and epigenetic modifiers appear to be especially large in arrhythmogenic cardiomyopathy. For example, a recent analysis of mutational heterogeneity, genetic modifiers, and environmental influences in 9 quantifiable traits in arrhythmogenic cardiomyopathy revealed that heritability ranged from only 20% (for ventricular arrhythmia grade) to 77% (for left ventricular ejection fraction and right-to-left volume ratio). Significant modifier gene effects were found to be the single most sensitive and specific diagnostic feature, even in patients without complete or incomplete right bundle-branch block. An r/s ratio of <1 in V1 was the best diagnostic indicator in patients with complete right bundle-branch block. Another study that appeared shortly before the 2010 classification was based on recent detailed studies of the ECG features of this highly arrhythmogenic disease spectrum.

**New ECG and Electroanatomic Features in Arrhythmogenic Cardiomyopathy**

ECG parameters are featured prominently in the 2010 diagnostic criteria. Previously, only the occurrence of epsilon waves and prolongation of the QRS (>100 milliseconds) in V1 to V3 were considered major criteria, whereas inverted T waves in the right precordial leads, late potentials on the signal-averaged ECG, left bundle-branch block–type ventricular tachycardia, and frequent (>1000 per 24 hours) ventricular extrasystoles were minor criteria. Epsilon waves, representing delay in depolarization of the right ventricular free wall and outflow tract, are highly specific for arrhythmogenic cardiomyopathy, and have even been observed to occur during ventricular tachycardia. However, like many of the 1994 diagnostic criteria, epsilon waves occur in only a minority of patients with disease. To maintain specificity but enhance sensitivity, specific quantitative abnormalities in repolarization and conduction and specific types of arrhythmias are now categorized as major or minor criteria, and in many cases, thresholds have been reduced (eg, >500 extrasystoles is now a minor criterion).

Modification of the ECG criteria in the 2010 classification was based on recent detailed studies of the ECG features of arrhythmogenic cardiomyopathy. One such study of 100 patients who met the 1994 criteria defined the sensitivity and specificity of ECG criteria in the presence or absence of right bundle-branch block. T-wave inversions in V1 to V3 were found to be the single most sensitive and specific diagnostic feature, even in patients without complete or incomplete right bundle-branch block. Another study that appeared shortly before the 2010 criteria were published analyzed 50 index patients who met the 1994 criteria and 33 additional patients who fell just short of this standard. Three new ECG criteria (prolonged terminal activation duration in V1 to V3, ventricular tachycardia with left bundle-branch block morphology and superior axis, and multiple ventricular tachycardia morphologies) were shown to improve diagnostic sensitivity, so that 23 of the 33 patients (70%) who failed to meet the 1994 criteria were reclassified. Only 1 of these patients exhibited epsilon waves, and the enhanced diagnostic yield was independent of the presence of a desmosomal gene mutation. Subsequently, the same group of investigators undertook a more formal analysis of the impact of the 2010 criteria. Of 105 patients who had originally been diagnosed by the 1994 criteria, 102 fulfilled the 2010 criteria. Pathogenic mutations were identified in 62 of the 105 patients in this group (59%). The new criteria also diagnosed 10 additional patients among 89 family members (of whom 9 carried PKP2 mutations) and 25 of 39 patients (64%) who had previously been classified as probable index patients on the basis of the 1994 criteria (14 of these 25 [56%] had desmosomal mutations). The 2 most important factors contributing to the enhanced diagnostic yield of the 2010 criteria were the modifications of the ECG criteria and the new genetic criterion.

Electroanatomic mapping in arrhythmogenic cardiomyopathy has been used to delineate anatomic correlates of diagnostic ECG features and to guide therapy. In a study of 17 patients with biopsy-proven disease, abnormalities on the signal-averaged ECG correlated most closely with low-voltage areas in the right ventricular outflow tract, whereas surface ECG abnormalities were associated with more diffuse right ventricular involvement. Delayed gadolinium enhancement on magnetic resonance imaging was also highly associated with the distribution of low-voltage areas. Percutaneous epicardial mapping has defined electroanatomic correlates of pathological observations, indicating that myocardial involvement in arrhythmogenic cardiomyopathy progresses from epicardium to endocardium. This feature, unique among the cardiomyopathies, may account in part for failed attempts to ablate ventricular tachycardia by endocardial approaches. At the same time, progressive right ventricular dilatation rather than progressive endocardial scarring has been observed in patients analyzed by sequential electroanatomic mapping studies, suggesting that therapeutic efforts to control right ventricular dilatation may be effective in long-term ventricular tachycardia control. Finally, despite the significant refinements in diagnosis, risk stratification in patients with arrhythmogenic cardiomyopathy remains imprecise, particularly in asymptomatic patients. Whereas a history of syncope or prior cardiac arrest is a proven indication for implantable cardioverter-defibrillator therapy, programmed ventricular stimulation traditionally used to stratify patients without spontaneous ventricular tachyarrhythmias has low predictive accuracy for identifying patients who will benefit from implantable cardioverter-defibrillator implantation.

**Disclosures**

None.

**References**

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Circulation. 2011;124:e390-e392
doi: 10.1161/CIRCULATIONAHA.111.064022
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/15/e390

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