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ARRHYTHMOGENIC CARDIOMYOPATHY: CONTEMPORARY CONCEPTS IN DIAGNOSIS, RISK STRATIFICATION, AND MANAGEMENT

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Abstract : Arrhythmogenic cardiomyopathy (ACM) is a genetically determined myocardial disease characterized by progressive fibrofatty replacement of the ventricular myocardium, ventricular arrhythmias, heart failure, and an increased risk of sudden cardiac death, particularly in young individuals and athletes. Contemporary understanding of ACM has evolved from a predominantly right ventricular disorder to a broader disease spectrum that includes biventricular and left-dominant phenotypes. Advances in molecular genetics, electrocardiography, cardiac magnetic resonance imaging, and genetic testing have significantly improved diagnostic accuracy and disease characterization. Despite these advances, ACM remains diagnostically and therapeutically challenging because of its heterogeneous clinical presentation and variable disease progression. Current management strategies focus on early diagnosis, risk stratification, prevention of malignant ventricular arrhythmias, lifestyle modification, pharmacological therapy, catheter ablation, and implantable cardioverter-defibrillator implantation. This review summarizes contemporary concepts in the pathophysiology, diagnosis, risk stratification, and evidence-based management of ACM, highlighting recent developments that are shaping modern clinical practice.

Keywords: arrhythmogenic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy; sudden cardiac death; ventricular arrhythmias; desmosomal mutations; cardiac MRI; risk stratification; implantable cardioverter-defibrillator.

Arrhythmogenic Cardiomyopathy is an inherited myocardial disorder characterized by progressive fibrofatty replacement of the ventricular myocardium, ventricular arrhythmias, structural cardiac abnormalities, and an increased risk of sudden cardiac death (SCD). Traditionally recognized as arrhythmogenic right ventricular cardiomyopathy (ARVC), the disease is now understood as a broader clinical spectrum involving the right ventricle, left ventricle, or both ventricles. This evolving concept has led to the adoption of the term arrhythmogenic cardiomyopathy, reflecting the heterogeneous phenotypic and genetic nature of the disease. ACM predominantly affects young adults and athletes and represents an important cause of exercise-related SCD. The disease is strongly associated with mutations in genes encoding desmosomal proteins, including plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and junction plakoglobin (JUP). Disruption of intercellular adhesion contributes to myocardial injury, inflammation, fibrosis, and electrical instability, ultimately predisposing patients to ventricular tachyarrhythmias and progressive ventricular dysfunction.

The diagnosis of ACM remains challenging because of incomplete penetrance, variable expressivity, and overlap with other cardiomyopathies and inflammatory myocardial diseases. Contemporary diagnostic evaluation relies on a multimodal approach integrating electrocardiography, echocardiography, cardiac magnetic resonance imaging (CMR), genetic testing, and standardized diagnostic criteria such as the Padua criteria. In recent years, significant

advances in cardiac imaging and molecular cardiology have improved early disease detection and risk assessment.

Management of ACM primarily focuses on the prevention of malignant ventricular arrhythmias and SCD. Current therapeutic strategies include lifestyle modification and exercise restriction, antiarrhythmic drug therapy, catheter ablation, implantable cardioverter-defibrillator (ICD) implantation, and treatment of heart failure in advanced stages. This review discusses contemporary concepts in the pathophysiology, diagnosis, risk stratification, and management of ACM, with emphasis on recent developments that are influencing modern clinical practice

Pathophysiology and Genetics

Arrhythmogenic Cardiomyopathy is primarily a genetically determined disorder of the cardiac desmosome, a specialized intercellular junction responsible for mechanical coupling and electrical stability between cardiomyocytes. Mutations involving desmosomal proteins impair cell-to-cell adhesion, rendering myocardial tissue vulnerable to mechanical stress, inflammation, and progressive structural remodeling. The disease is most commonly associated with pathogenic variants in plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and junction plakoglobin (JUP), although non-desmosomal mutations have also been increasingly recognized. Under physiological conditions, desmosomes maintain myocardial integrity during repetitive mechanical contraction. In ACM, defective desmosomal signaling leads to cardiomyocyte detachment and death, followed by inflammatory responses and replacement of normal myocardium with fibrofatty tissue. This pathological remodeling predominantly affects the right ventricle; however, left ventricular and biventricular involvement are increasingly identified with advanced imaging techniques and genetic analysis.

The fibrofatty replacement process creates areas of slow electrical conduction and conduction heterogeneity, thereby establishing a substrate for re-entrant ventricular arrhythmias. These electrophysiological abnormalities contribute to ventricular tachycardia, ventricular fibrillation, and sudden cardiac death, which may occur even in the early stages of disease before overt structural abnormalities become evident. Exercise and sustained adrenergic stimulation are believed to accelerate disease progression by increasing mechanical stress on structurally fragile myocardium, explaining the higher incidence of arrhythmic events among athletes.

Recent evidence also highlights the role of myocardial inflammation, apoptosis, and altered intracellular signaling pathways in ACM progression. Inflammatory episodes may mimic myocarditis clinically and radiologically, complicating the diagnostic process. Furthermore, genotype-phenotype variability and incomplete penetrance contribute to the broad clinical spectrum of ACM, ranging from asymptomatic mutation carriers to severe arrhythmogenic and heart failure phenotypes. Advances in molecular cardiology continue to improve understanding of disease mechanisms and may provide future opportunities for targeted and gene-specific therapies.

Clinical Presentation

Arrhythmogenic Cardiomyopathy demonstrates a highly variable clinical presentation ranging from asymptomatic disease to malignant ventricular arrhythmias, progressive heart failure, and

sudden cardiac death (SCD). Clinical manifestations often develop during adolescence or early adulthood, although disease onset and severity vary considerably depending on genetic background, environmental influences, and the extent of ventricular involvement.

Palpitations are among the most common presenting symptoms and are usually associated with premature ventricular contractions or sustained ventricular tachycardia. Patients may also experience dizziness, presyncope, or syncope secondary to transient hemodynamic instability caused by ventricular arrhythmias. Syncope, particularly when exercise-related or unexplained, is considered a clinically significant marker associated with increased arrhythmic risk and potential SCD. Ventricular arrhythmias in ACM typically originate from areas of fibrofatty myocardial replacement and frequently demonstrate left bundle branch block morphology due to right ventricular involvement. However, left-dominant and biventricular phenotypes may produce more diverse electrocardiographic patterns. In some individuals, SCD may represent the first clinical manifestation of disease, particularly among young athletes exposed to intense physical activity and adrenergic stress.

As the disease progresses, structural and functional ventricular abnormalities may lead to symptoms of right-sided, left-sided, or biventricular heart failure. Patients can develop exertional dyspnea, fatigue, peripheral edema, and reduced exercise tolerance. Advanced disease stages are associated with progressive ventricular dysfunction, recurrent ventricular tachyarrhythmias, atrial arrhythmias, and thromboembolic complications. Importantly, ACM exhibits incomplete penetrance and marked phenotypic heterogeneity. Some mutation carriers remain asymptomatic for years despite detectable genetic abnormalities, whereas others rapidly progress to severe arrhythmic or heart failure phenotypes. This variability highlights the importance of careful family screening, longitudinal follow-up, and individualized risk assessment in affected patients and their relatives.

Diagnostic Approaches

The diagnosis of Arrhythmogenic Cardiomyopathy remains challenging because of its heterogeneous clinical presentation, variable penetrance, and overlap with other cardiomyopathies and inflammatory myocardial diseases. Consequently, contemporary diagnosis relies on an integrated multimodal approach that combines clinical evaluation, electrocardiography, cardiac imaging, genetic testing, and standardized diagnostic criteria.

Electrocardiography

Electrocardiography (ECG) represents a fundamental component of ACM evaluation. Common findings include T-wave inversions in the right precordial leads, epsilon waves, prolonged terminal activation duration, and ventricular arrhythmias with left bundle branch block morphology. Signal-averaged ECG may reveal late potentials reflecting delayed ventricular conduction. Holter monitoring is also important for detecting premature ventricular contractions, nonsustained ventricular tachycardia, and arrhythmic burden.

Echocardiography

Transthoracic echocardiography is widely used as an initial imaging modality for structural and functional assessment. Echocardiographic abnormalities may include right ventricular dilation, regional wall motion abnormalities, aneurysm formation, and reduced ventricular systolic function. However, early-stage disease may demonstrate subtle or absent echocardiographic findings, limiting sensitivity in some patients.

Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance Imaging has emerged as a cornerstone in ACM diagnosis because of its superior ability to evaluate ventricular morphology, function, and myocardial tissue characterization. CMR can identify fibrofatty infiltration, regional wall motion abnormalities, ventricular aneurysms, and late gadolinium enhancement indicative of myocardial fibrosis. Additionally, CMR is particularly valuable for detecting left ventricular and biventricular phenotypes that may be underrecognized by conventional imaging techniques.

Genetic Testing

Genetic testing plays an increasingly important role in confirming diagnosis, identifying at-risk relatives, and improving understanding of disease mechanisms. Pathogenic variants involving desmosomal genes such as PKP2, DSP, DSG2, DSC2, and JUP are frequently identified. Nevertheless, interpretation of genetic findings requires careful clinical correlation because incomplete penetrance and variants of uncertain significance may complicate diagnostic evaluation.

Endomyocardial Biopsy and Diagnostic Criteria

Endomyocardial biopsy may demonstrate characteristic fibrofatty myocardial replacement; however, its clinical utility is limited by sampling error and procedural invasiveness. To improve diagnostic standardization, contemporary evaluation commonly utilizes the Padua criteria, which integrate structural, electrocardiographic, arrhythmic, histopathological, and genetic findings. These criteria expanded earlier Task Force Criteria by incorporating left ventricular phenotypes and advanced imaging features, thereby improving diagnostic sensitivity and specificity across the broad ACM spectrum.

Risk Stratification

Risk stratification in Arrhythmogenic Cardiomyopathy is primarily focused on identifying patients at high risk of malignant ventricular arrhythmias and sudden cardiac death (SCD), with the goal of guiding preventive strategies such as implantable cardioverter-defibrillator (ICD) therapy and lifestyle modification.

The most important predictors of arrhythmic risk include a history of sustained ventricular tachycardia, previous cardiac arrest, and unexplained syncope, particularly when occurring during exertion. The burden of ventricular ectopy, especially frequent premature ventricular contractions or non-sustained ventricular tachycardia on Holter monitoring, is also strongly associated with increased risk. Additionally, the presence of right or left ventricular dysfunction on imaging studies reflects advanced structural disease and correlates with a higher probability of life-threatening

arrhythmias. Cardiac magnetic resonance imaging plays a key role in risk assessment by identifying late gadolinium enhancement, which reflects myocardial fibrosis and serves as a substrate for re-entrant ventricular arrhythmias. Left ventricular involvement, even in patients initially classified as right-dominant disease, has been associated with a worse prognosis and higher arrhythmic risk. Similarly, extensive disease involving both ventricles indicates a more advanced phenotype with increased clinical risk.

Exercise exposure is an important modifiable risk factor. High-intensity endurance exercise has been shown to accelerate disease progression and increase arrhythmic events in genetically predisposed individuals. Therefore, restriction from competitive or high-intensity sports is recommended in most patients with ACM, particularly those with confirmed pathogenic mutations or established structural disease. Recent approaches to risk stratification incorporate multivariable prediction models that integrate clinical, electrocardiographic, imaging, and genetic data to estimate individualized SCD risk. These models assist in selecting candidates for primary prevention ICD implantation, which remains the most effective intervention for preventing SCD in high-risk patients.

Therapeutic Approaches

Management of Arrhythmogenic Cardiomyopathy is primarily aimed at preventing sudden cardiac death, reducing ventricular arrhythmia burden, and managing progressive ventricular dysfunction. Current therapeutic strategies are individualized based on symptom severity, arrhythmic risk profile, and degree of structural heart disease. Exercise restriction is a cornerstone of therapy; patients are advised to avoid high-intensity and competitive endurance sports, as sustained mechanical stress has been shown to accelerate disease progression and increase arrhythmic risk, while low-to-moderate intensity physical activity may be allowed in selected stable patients under clinical supervision. Pharmacological therapy includes antiarrhythmic drugs to reduce ventricular arrhythmias and symptoms; beta-blockers are commonly used to reduce adrenergic stimulation and suppress ventricular ectopy, while amiodarone or sotalol may be considered in refractory cases, although long-term efficacy is variable. Catheter ablation is indicated in patients with recurrent monomorphic ventricular tachycardia despite optimal medical therapy, but recurrence is relatively common due to the progressive and diffuse nature of the disease and the presence of multiple arrhythmogenic substrates. Implantable cardioverter-defibrillator (ICD) therapy remains the most effective intervention for preventing sudden cardiac death in high-risk patients, including survivors of cardiac arrest, patients with sustained ventricular tachycardia, and selected individuals identified through risk stratification models for primary prevention. In advanced stages with severe biventricular dysfunction, patients may develop refractory heart failure requiring advanced therapies, and heart transplantation represents the definitive treatment option for carefully selected patients with end-stage disease and recurrent malignant arrhythmias.

Conclusion

Arrhythmogenic Cardiomyopathy is a complex and progressive myocardial disorder characterized by significant genetic heterogeneity, variable phenotypic expression, and a strong association with ventricular arrhythmias and sudden cardiac death. Advances in molecular genetics,

multimodal imaging, and standardized diagnostic criteria have significantly improved early recognition and classification of the disease spectrum, including right-dominant, left-dominant, and biventricular forms. Despite major progress in understanding its pathophysiology and clinical behavior, ACM remains a challenging condition in terms of early diagnosis, risk stratification, and long-term management. Contemporary therapeutic strategies primarily focus on preventing malignant arrhythmias, reducing sudden cardiac death risk, and managing heart failure progression through a combination of lifestyle modification, pharmacological therapy, catheter ablation, and implantable cardioverter-defibrillator implantation. Future developments in precision medicine, genotype-guided therapy, and advanced imaging techniques are expected to further refine patient management and improve outcomes in this high-risk population.

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