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Risk stratification in arrhythmogenic cardiomyopathy: scoring or personalized medicine?

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Almost 40 years after the description of arrhythmogenic cardiomyopathy (ACM), arrhythmic risk stratification remains central to patient management. Antiarrhythmic therapy may involve the use of antiarrhythmic drugs as well as invasive tools such as catheter ablation, with the implantation of an implantable cardioverter defibrillator being of utmost importance. Given the wide phenotypic variability of ACM, the first step in arrhythmic risk stratification requires a thorough assessment of clinical, morphological, and electrical parameters. Moreover, in the last years, genetic testing has become increasingly important, not only for family screening but also in determining prognosis. Finally, data from large series of ACM patients have led to the creation of risk calculators, which are now available online for the medical community. While newly available methods for stratifying arrhythmic risk can be useful, the thoughtful clinical decision-making by clinicians with specific expertise in cardiomyopathies remains of fundamental importance. Additionally, as ACM is a progressive disease, arrhythmic risk stratification should be periodically revised based on newly emerging clinical and instrumental parameters.

Introduction

Almost 40 years after the description of arrhythmogenic cardiomyopathy (ACM), arrhythmic risk stratification remains central to patient management. Despite being considered a rare disease, ACM has consistently been reported as one of the leading causes of sudden cardiac death (SCD), particularly among young athletes.[1] However, the arrhythmic burden of the disease remains significant even in patients with later-onset disease, with sustained ventricular tachycardia (SVT) being the most frequent presentation in individuals over 40 and 50 years of age.[2] According to the natural history of the disease, life-threatening ventricular arrhythmias (VAs) can occur in the early stages, even before an overt phenotypic presentation is apparent, making the use of the full diagnostic and prognostic armamentarium crucial.[3]

Diagnostic tools

Considering the wide phenotypic variability of ACM, it is essential to emphasize that the first step in arrhythmic risk stratification is an accurate and precise diagnosis. Beside investigations of previous arrhythmic symptoms, the clinician's role is to actively pursue all diagnostic findings,[3] starting with the detection of electrocardiogram (ECG) abnormalities and to maintain a high index of suspicion, particularly in subtle or atypical cases. It is crucial not only to quantify the number and complexity of VA in 24-h Holter monitoring

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but also to investigate the morphologies of premature ventricular contractions (PVCs). This allows for the evaluation of arrhythmia morphology and, consequently, the probable site of origin. For this reason, the Holter ECG should possibly be a 12-lead system. Furthermore, the behaviour of PVCs during an exercise stress test should be carefully evaluated.

The role of electrophysiological (EP) study in arrhythmic risk stratification is highly debated, as much of the evidence comes from studies involving clinically heterogeneous cohorts, which have provided conflicting results. Recently, a study on ACM patients without previous overt arrhythmic events demonstrated that SVT induction during EP study was associated with a significant increase of sustained VA episodes during follow-up.[4]

Regarding imaging modalities, echocardiography is the first-line imaging tool and should not be limited to evaluating standard parameters such as biventricular dimensions and function. To improve diagnostic accuracy, it should incorporate advanced techniques, including 3D volume quantification and speckle-tracking analysis. In the presence of clinical suspicion and for family member evaluation, cardiac magnetic resonance (CMR) should always be performed, as it is the only imaging modality capable of providing a detailed assessment of ventricular dimensional, kinetic abnormalities, and tissue characterization. The detection of myocardial fibrosis plays a crucial role in risk stratification, particularly in patients with specific gene mutations. Beyond serving as a marker of electrical instability, fibrosis, along with altered values of advanced parameters such as T1 and T2 mapping and extracellular volume assessment, has been linked to an elevated risk of heart failure (HF).[5]

Lastly, endomyocardial biopsy can play a role in the differential diagnosis of inflammatory cardiomyopathies.[1,3]

Genetic testing

A positive genetic test not only contributes to the diagnostic criteria for disease detection but also, thanks to an improved understanding of genotype–phenotype correlations, provides the clinician with a valuable tool for managing arrhythmic risk stratification. Given the hereditary nature of the disease, identifying pathogenic or likely pathogenic variants in desmosomal genes, such as plakophilin-2 (PKP2) and desmoplakin (DSP), allows for early and accurate diagnosis, even before the onset of clinical symptoms. Pathogenic PKP2 variants are the most common genetic cause of ACM, frequently associated with a classic right-dominant or biventricular phenotype. Individuals with PKP2 mutations are at high risk for VA, with SVT and SCD often being early manifestations of the disease. In contrast, DSP mutations tend to result in left-dominant (or sometimes biventricular) cardiomyopathy, characterized by progressive subepicardial fibrosis and increased arrhythmic burden. Furthermore, some patients with ACM may present with phenotypic manifestations that overlap with those of dilated cardiomyopathy, such as those associated with the Filamin C mutation. Additionally, a significant proportion of ACM cases are gene elusive, which makes family screening more challenging.

Incorporating genetic testing into the diagnostic pathway not only aids in identifying individuals at risk of SCD but also enables a more precise approach to disease management, ranging from early-stage surveillance to lifestyle modifications and advanced therapeutic interventions. Thus, the integration of genetic data is critical for the accurate diagnosis, prognosis, and familial management of ACM.

Hot phases

Hot phases in ACM refer to episodes resembling myocarditis, characterized by chest pain, electrocardiographic changes, and troponin release, occurring in the absence of coronary artery disease.[6] These episodes are believed to represent acute inflammatory responses within the myocardium and are often associated with the presence of gene mutations, particularly of desmosomal gene DSP. The presence of myocardial fibrosis and inflammation during these phases suggests an active role in disease progression, contributing to both structural and electrical instability. Hot phases are more commonly observed in younger patients and are frequently linked to left-dominant ACM, although they can occur across the entire ACM spectrum. Despite their clinical significance, the exact prognostic implications of hot phases, particularly regarding arrhythmic risk and HF, remain under investigation, necessitating further research to optimize patient management and risk stratification.

Therapy

Medical treatment

Patients with ACM typically exhibit a high prevalence of VA and antiarrhythmic drugs are commonly used. However, pharmacological therapy plays a limited role, especially in long-term management and in preventing disease progression.[7] While beta-blockers are considered the first-line therapy for patients with VA due to their ability to reduce adrenergic tone, there are conflicting data regarding the efficacy of other antiarrhythmic drugs, such as amiodarone, sotalol, and flecainide. These medications are often used when beta-blockers alone fail to adequately control the arrhythmic burden.[7]

Physical activity

Avoiding high-intensity physical activity is a Class I recommendation for patients with a definite diagnosis of ACM, making it an integral part of disease management.[8] This is because high-intensity exercise increases phenotypic expression, exacerbates the arrhythmic burden, and contributes to the development of ventricular dysfunction.[9] Different studies have shown that exercise can accelerate disease progression by promoting fibrofatty replacement of the myocardium, particularly in individuals with a genetic predisposition. This remodelling process increases the substrate for VA, leading to a higher incidence of ventricular tachycardia (VT) and SCD. Furthermore, endurance sports have been associated with an earlier onset of symptoms and more severe structural abnormalities. Data suggest that prolonged exercise may amplify mechanical stress on desmosomes, impairing cell-to-cell adhesion and triggering myocyte detachment and death, which in turn

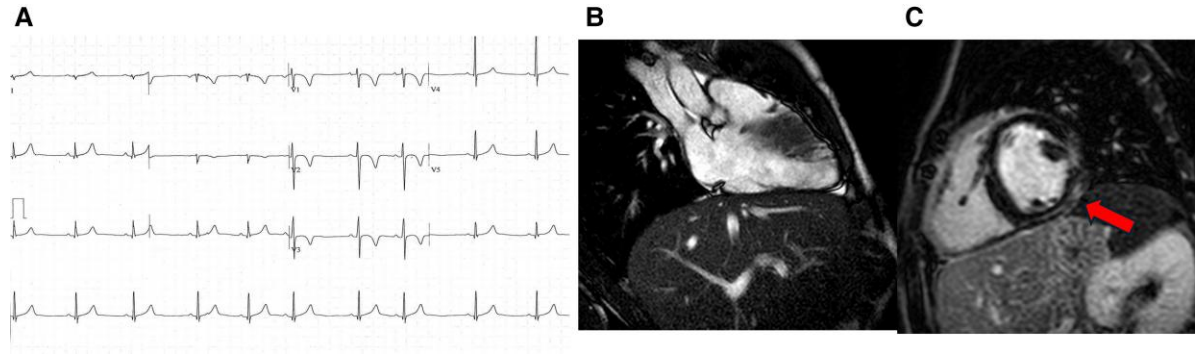

Figure 1 A 15-year-old patient with a pathogenic plakophilin-2 mutation. (*A*) Twelve-lead electrocardiogram showing deep T-wave inversions in the right precordial leads. (*B*) Cardiac magnetic resonance steady-state free precession still-cine imaging demonstrating right ventricular dilatation. (*C*) Phase-sensitive inversion recovery sequences revealing left ventricular involvement with evidence of fibrosis. Using the arrhythmogenic right ventricular cardiomyopathy risk score, the estimated 5-year risk of sustained ventricular arrhythmias was 38.7%, placing the patient in a high-risk category.

exacerbates inflammation and fibrosis. Therefore, exercise restriction is crucial in reducing arrhythmic events and improving long-term outcomes in ACM patients.

Catheter ablation

For patients who have not responded to anti-arrhythmic medical therapy, catheter ablation has emerged as a valuable therapeutic option to reduce the burden of VT and decrease interventions from implantable cardioverter defibrillators (ICDs).[7] In patients with right dominant or biventricular forms of ACM, invasive management with VT ablation has proven effective in reducing the arrhythmic burden. Pre-procedural imaging, such as cardiac magnetic resonance or computed tomography, should be routinely implemented to identify myocardial scarring, enhance procedural planning, and ensure safe access. Given the predominantly epicardial location of the arrhythmic substrate in ACM patients, obtaining epicardial access is essential for effective treatment. High-density electroanatomic mapping, such as density and epicardial electroanatomic mapping, combined with programmed VT stimulation, allows clinicians to precisely identify the critical areas of arrhythmic substrate, resulting in more accurate ablation and improved outcomes.

Implantable cardioverter defibrillator implantation and development of risk calculators

While pharmacological therapy and catheter ablation may help control VA, ICDs remain the only proven intervention for reducing the risk of SCD in patients with ACM.[7] However, given the young age of many patients who require an ICD, careful consideration of the risks and benefits is crucial before proceeding with implantation. In fact, in a multinational cohort of patients with ACM, nearly one-third experienced the combined endpoint of inappropriate shocks or surgical complications.[10]

In 2015, a systematic approach to arrhythmic risk stratification was attempted, resulting in the identification of three risk categories.[11] The high-risk group, with a 10% incidence of life-threatening arrhythmic events, primarily included patients with severe right ventricular dysfunction and those indicated for secondary prevention. In contrast, the low-risk category encompassed phenotype-negative patients, in which ICD was not recommended.

In the more controversial intermediate-risk category, major risk factors such as syncope, non-SVT (NSVT), and moderate right ventricular dysfunction have been identified as primary considerations for ICD implantation.

Recently, a prediction model for primary prevention in ACM patients was proposed, based on a multicentric cohort of 528 patients, to estimate the risk of events over a 5-year period.[12]

The study demonstrated that NSVT, cardiac syncope, and a reduction in right ventricular ejection fraction—but interestingly not left ventricular ejection fraction—were associated with an increased risk, alongside male sex, increasing age (per year), 24-h PVC count, and the extent of negative T waves at ECG (*Figure 1* provides an example of the application of the arrhythmogenic right ventricular cardiomyopathy risk calculator). An additional international study evaluated the performance of the risk calculator in a cohort of ACM patients, stratified by genetic mutation.[13] While the calculator demonstrated good performance in the PKP2 mutation group, where it was mostly primarily validated, its performance was significantly less effective in the gene-elusive group. In patients with DSP mutations, the variables incorporated in the calculator were not associated with an increased risk of events. However, the presence of fibrosis on CMR and a reduced LVEF that were not included in the model were linked to a higher risk of adverse events.

Consequently, a new risk calculator was developed based on a multicentre study of 471 DSP patients followed for a median of 4.0 years; of these, 71 experienced first sustained VA events (2.6% events/year). Five clinical parameters were identified as independent predictors of VA and were included in a novel DSP risk score: female sex, history of NSVT, natural logarithm of 24-h PVCs burden, LVEF < 50%, and presence of moderate to severe right ventricular systolic dysfunction (*Figure 2* provides an example of the application of the DSP risk calculator). The model demonstrated good risk discrimination within both the development and external validation cohorts.[14]

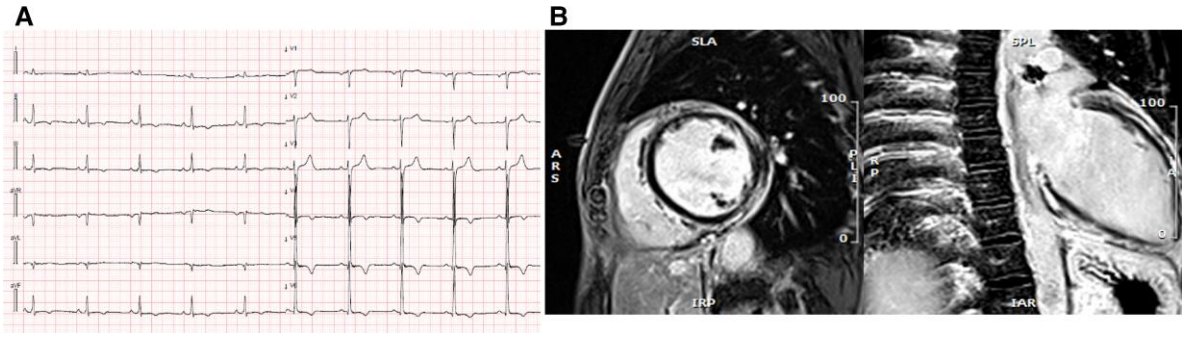

Figure 2 A 37-year-old patient with a pathogenic desmoplakin mutation. (*A*) Twelve-lead electrocardiogram showing diffuse T-wave inversions. (*B*) Cardiac magnetic resonance in short-axis and two-chamber long-axis phase-sensitive inversion recovery sequences, demonstrating diffuse epicardial gadolinium enhancement with mildly impaired function. The application of the desmoplakin risk score estimates a 5-year risk of sustained ventricular arrhythmias at 21%, indicating a high-risk category.

While newly available methods for stratifying arrhythmic risk can be useful, the thoughtful clinical decision-making by clinicians with specific expertise in cardiomyopathies remains of fundamental importance. There are no substitutes for the complex process of a comprehensive clinical assessment based on specialized knowledge.[15] For this reason, arrhythmic risk stratification should involve a multidisciplinary discussion among the clinician, electrophysiologist, and geneticist.

Conclusions

Arrhythmogenic cardiomyopathy is characterized by significant phenotypic variability, which the clinician must carefully consider in patient management. While the risk calculator provides valuable support for arrhythmic risk stratification, it should be used as part of a comprehensive patient assessment, not in isolation.[15]

Furthermore, beside medical and invasive antiarrhythmic therapy, the modulating role of physical activity is crucial for managing disease progression and arrhythmic risk.

In addition, as a progressive disease, arrhythmic risk stratification should be periodically revised based on newly emerging clinical, morphological, and electrical parameters.

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Data availability

No new data were generated or analysed in support of this research.

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