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Review

Pathogenesis of Arrhythmogenic Cardiomyopathy

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ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) is a primary myocardial disease. It is characterized by frequent ventricular arrhythmias and increased risk of sudden cardiac death typically arising as an early manifestation before the onset of significant myocardial remodelling. Myocardial degeneration, often confined to the right ventricular free wall, with replacement by fibrofatty scar tissue, develops in many patients. ACM is a familial disease but genetic penetrance can be low and disease expression is highly variable. Inflammation might promote disease progression. It also appears that exercise increases disease penetrance and accelerates its development. More than 60% of probands harbour mutations in genes that encode desmosomal proteins, which has raised the possibility that defective cell-cell adhesion might play a role in disease pathogenesis. Recent advances have implicated changes in the canonical wingless-type mouse mammary tumour virus integration site (Wnt)/β-catenin and Hippo signalling pathways and defects in forwarding trafficking of ion channels and other proteins to the intercalated disk in cardiac myocytes. In this review we summarize the current understanding of the pathogenesis of ACM and highlight future research directions.

RÉSUMÉ

La cardiomyopathie arythmogène (CMA) est une maladie myocardique primitive. Elle est caractérisée par de fréquentes arythmies ventriculaires et l'augmentation du risque de mort cardiaque subite se manifestant typiquement de manière précoce avant l'apparition d'un remodelage myocardique significatif. La dégénération myocardique, souvent limitée à la paroi libre du ventricule droit, avec le remplacement du tissu cicatriciel fibro-adipeux, se développe chez plusieurs patients. La MCA est une maladie familiale, mais la pénétrance peut être faible et l'expressivité de la maladie est très variable. L'inflammation favoriserait la progression de la maladie. Il semble également que l'exercice augmente la pénétrance de la maladie et accélère son développement. Plus de 60 % des proposants portent des mutations dans les gènes qui encodent les protéines desmosomales, ce qui soulève la possibilité que l'adhérence cellule-cellule défectueuse puisse jouer un rôle dans la pathogenèse de la maladie. De récentes avancées ont impliqué des changements dans les voies de signalisation Wnt/ β-caténine (voie canonique) et Hippo et des anomalies en transférant le trafic des canaux ioniques et les autres protéines au disque intercalé dans les myocytes cardiaques. Dans cette revue, nous résumons les connaissances actuelles sur la pathogenèse de la MCA et dégageons les orientations futures de la recherche.

It was not until 1982 that Frank Marcus and Guy Fontaine with others reported the first detailed description of 24 patients with what they called "arrhythmogenic right ventricular dysplasia," which, they postulated, originated as a developmental anomaly of the right ventricle (RV).[1] It has since been recognized that this disease falls within the spectrum of the nonischemic cardiomyopathies classified by the World Health Organization in 1994.[2] The designation "arrhythmogenic right ventricular cardiomyopathy" (ARVC) reflected the preferential involvement of the RV in many cases. However, the more recent recognition of left-dominant and biventricular forms has led to adoption of the broader term, "arrhythmogenic cardiomyopathy" (ACM).[3]

ACM is estimated to affect 1:1000-1:5000 individuals in the general population.[4] It is among the most common causes of sudden cardiac death (SCD) in people 35 years of age or younger.[3] The actual prevalence might be greater because the diagnosis might be missed clinically and at postmortem examination. Its cardinal feature is the early predisposition to ventricular arrhythmias and SCD typically arising in the context of well-preserved ventricular structure and function. Thus, in its early stages, ACM is more reminiscent of the ion channelopathies than the other nonischemic cardiomyopathies.[5]

As the disease evolves, the ventricular myocardium exhibits progressive degeneration of cardiac myocytes with replacement by fat and fibrous tissue. The pattern and distribution of myocardial degeneration are highly characteristic and distinctly different than that seen in other cardiomyopathies.[6] In contrast to the tendency for greater involvement of subendocardial muscle in various forms of heart disease associated with hypertrophy, it is the subepicardium of the RV free wall that is most commonly affected in ACM. Moreover, segments of the

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RV free wall that experience the greatest mechanical stress during the cardiac cycle—the posterior segment below the tricuspid annulus, the apex, and the RV outflow tract—show the greatest damage. In general, the endocardial trabeculated muscles of the RV and the interventricular septum are spared. When the left ventricle (LV) is involved, myocardial degeneration and fibrosis are most conspicuous in the subepicardium and midmyocardium of the lateral free wall.[6]

Originally, 2 pathological forms of the disease were proposed: fatty and fibrofatty.[7] However, it is now recognized that significant ingrowth of epicardial adipocytes might occur in the RV in elderly or obese individuals which, in extreme cases, can extend focally to the endocardial surface and at least superficially resemble the picture seen in ACM. Therefore, infiltration of adipose tissue without inflammation and myocyte degeneration is no longer considered diagnostic of ACM. Instead, histologic features of myocyte degeneration/death and fibrosis, with or without fat, in a specific distribution, are considered the most reliable histopathological indicators of the disease.[6] Another typical feature is mononuclear inflammation, mainly lymphocytic, which might be extensive and associated with areas of myocyte degeneration, creating a picture similar to that seen in viral myocarditis. The role of inflammation in ACM remains largely undefined. It has been proposed that inflammatory infiltrates might extend injury to previously unaffected regions of the myocardium, a process associated with episodic exacerbations characterized by more severe electrocardiographic abnormalities, increased symptomatic arrhythmias causing dizziness, palpitations, and syncope. Such a clinical picture might be misdiagnosed as myocarditis.[3]

The natural history of classical right-sided ACM is divided into 4 stages. In the initial or concealed phase, there are minimal or no structural abnormalities. Yet, the patient is at risk of SCD. The second phase is characterized by ventricular arrhythmias of left bundle branch block morphology and structural changes, typically confined to the RV, which can be observed using echocardiography, angiography, and/or magnetic resonance imaging. During this phase, patients might experience syncope and/or palpitations. The third phase is defined by overt RV failure with overall preserved LV function. The final phase is marked by overt LV involvement and biventricular heart failure. Left dominant ACM is characterized by primary (but not necessarily exclusive) LV involvement, and biventricular ACM is defined by early and parallel involvement of both ventricles.[3]

The clinical diagnosis of ACM remains challenging because of its age-related progression, vast phenotypic variation, and incomplete penetrance. No single gold-standard diagnostic test exists. Instead, diagnosis relies on a scoring system first introduced in 1994 with "major" and "minor" criteria from categories including structural changes, electrocardiographic changes, family history, arrhythmias, and tissue pathology.[2] Although these so-called "Task Force Criteria" are relatively specific, they are not highly sensitive. Diagnostic power was increased in the revised 2010 criteria in which genetic criteria and more quantification of metrics allowing for greater discrimination and identification of earlier/milder forms of ACM were included.[8]

A number of diseases might mimic ACM rendering its diagnosis even more challenging. Early ACM can be misdiagnosed as idiopathic right ventricular outflow tract (RVOT) tachycardia[9] or Brugada syndrome.[10] Nevertheless, current research indicates that idiopathic RVOT tachycardia might not be as benign as originally thought.[11] There is also evidence that Brugada syndrome might also involve structural abnormalities of the RVOT.[12] In the advanced biventricular form, ACM is almost impossible to distinguish from dilated cardiomyopathy (DCM). As already mentioned, ACM might also mimic myocarditis and vice-versa.[13] Sarcoidosis is a well-known phenocopy of ACM. Patients with sarcoid might present with many features considered to be highly diagnostic of ACM including inverted T-waves in right precordial leads, ventricular tachycardia of left bundle branch block morphology, RV abnormalities seen using various imaging modalities, late potentials, and >2000 premature ventricular contractions observed using 24-hour Holter monitoring. Differential diagnosis typically relies on a heart biopsy showing noncaseating granulomas or other features of sarcoidosis not seen in ACM including hilar lymphadenopathy with uptake of ^{22}F-2deoxyglucose using positron emission tomography.[14] Other pathologies that mimic ACM include pulmonary hypertension and Uhl's anomaly. The revised Task Force Criteria provide cutoff values for RV imaging and histopathological changes, which facilitates differential diagnosis.[8]

That exercise might lead to more adverse events in ACM has been recognized for many years but until recently the evidence has been largely circumstantial.[15] In 1995 Marcus and Fontaine reported that SCD in subjects with ARVC often occurs during exercise.[16] They attributed this to the fact that exercise causes significant stretching of the RV and a disproportionate increase in RV afterload after exercise, which, they thought, promoted ventricular arrhythmias.[17] In a subsequent study published in 2005 from Johns Hopkins University, it was reported that physical activity was part of the daily life of 49% of their ACM patients, 50% of whom were female.[18] The striking male predominance in the disease in Europe could be related at least in part to a greater proportion of men who engage in exercise in Europe.[19] A larger study conducted at Johns Hopkins showed that earlier disease onset (younger than 25 years of age) was significantly associated with intense exercise. In the same study it was also suggested that exercise could be a trigger for disease manifestation in previously unaffected mutation carriers and could accelerate disease progression.[20]

ACM management is focused mainly on SCD prevention. Young competitive athletes with ACM have a 5.4-fold increased risk of SCD compared with nonathletes.[21] Probands and relatives who manifest disease-related abnormalities are, therefore, advised to avoid competitive sports and endurance training. Implantable cardiac defibrillators are being used increasingly for primary prevention in cases of definite ACM. Antiarrhythmic pharmacological agents and catheter ablation are also used to reduce the arrhythmic burden. Cardiac transplantation, although relatively unusual in this disease spectrum, is an option in patients with incessant ventricular tachycardia (VT) or end-stage heart failure.[3]

Genetics of ACM

Adherens junctions and desmosomes are intercellular adhesion complexes which, in cardiac myocytes, reside within