ARRHYTHMOGENIC CARDIOMYOPATHY: GENETIC PATHOLOGY, INFLAMMATORY SYNDROME, OR BOTH?

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ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) affects mainly young athletes <35 years old and has a potential risk of malignant arrhythmias and sudden death. Different post-mortem and clinical studies have been conducted in North America, Asia, and Europe, with sharp differences in incidence and sex-associated pattern. Alterations in desmosome proteins, such as desmoglein, plakophilin, ion channels, or intracellular calcium handling proteins, have been highlighted as the principal cause of ACM, but the pathology has shown more complexity than initially described. This short review summarises the principal and more recent findings about ACM, mainly those related to inflammatory phenomena reported in the literature. Viral infections, especially enterovirus, have been associated with ACM and may be implicated in myocardial apoptosis, structural cardiac changes, and sudden death. Bartonella henselae and Sarcocystis infection have additionally been reported in ACM patients. Information regarding the role of proinflammatory cytokine or T cell infiltration and their possible role in sudden death is scarce, with increasing evidence of proinflammatory infiltrate associated with fibro-fatty ventricular patches related to biventricular affectation and worse outcomes. Nevertheless, findings taken from other sudden death-causing cardiomyopathies, such as viral myocarditis and Chagas disease, allow us to propose proinflammatory cytokines, such as tumour necrosis factor and interleukins 17 and 2, as possible serological markers of sudden death and/or ventricular dysfunction in order to conduct further research and identify diagnosis/prognosis markers for ACM.

Keywords: Arrhythmogenic cardiomyopathy (ACM), arrhythmias, sudden death.

INTRODUCTION

Historical Antecedents and Definition

Arrhythmogenic cardiomyopathy (ACM), previously called arrhythmogenic right ventricular cardiomyopathy or arrhythmogenic right ventricular dysplasia, was classically defined as a fibro-fatty substitution of ventricular myocardium. Recent advances have given a more complete view of its pathophysiology, including genetic and electrophysiological criteria to classify the disease. Therefore, we can consider ACM as a ventricular arrhythmogenic syndrome with a structural substrate associated to intercalated disc protein mutations. The possible role of ionic disturbances in lethal arrhythmias make it challenging to specify a precise definition and adopt a rational approach to prevention and therapeutics and this should be acknowledged.

Initially, ACM was reported mainly in the right ventricle,1 but may also implicate the left ventricle, as well as both ventricles simultaneously. ACM principally affects young men and can cause sudden death by ventricular arrhythmias,2 especially in athletes, which is not always associated to structural changes in ventricular walls. As a result of these variables, we can classify ACM into ionic and non-ionic-associated origin by the presence or absence of structural ventricular changes. In this review, we explore the possible role of inflammation as a concomitant cause in ACM, a mechanism poorly explored in the literature and one that possibly should be included in further classifications.
ACM was first described early in the 1980s. Initially, it was reported as hypokinetic cardiomyopathy associated with non-ischaemic tachycardia.\(^1\) Progressively, ACM was described as being in association with lethal arrhythmias,\(^3\) functional myocardial involvement,\(^4\) and biventricular affection.\(^5,6\) The clinical and electrocardiographic spectrum of ACM was described by Nava et al.\(^7,8\) as well as the genetic involvement in arrhythmia genesis.\(^9,13\) In the next sections, we briefly describe the most recent advances in the comprehension of the pathophysiology of ACM.

**Predisposing Factors**

**Sex, physical activity, and incidence**

ACM incidence patterns have been addressed by several authors. A French study reported ACM in 2.8% of 361 autopsies of sudden cardiovascular death.\(^14\) A 2016 multicentre European Cardiomyopathy Pilot Registry (1,155 patients) reported an incidence of 5.29% among all cardiomyopathy phenotypes studied.\(^15\) There are several differences reported in ACM clinical presentation, especially regarding sex-dependent patterning. In a study published in 2008, male patients had a higher incidence of sustained ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest as initial manifestations, with larger epicardial right ventricle unipolar low-voltage zone, and longer local abnormal ventricular activity.\(^16\) In another study, the sexes differed in prevalence of abnormal electrocardiogram (ECG) (69% versus 52%) and presence of late potentials; men had larger right ventricular dimensions and practised competitive sports more frequently.\(^17\) However, the same study reported that sex was not associated with a high incidence of life-threatening ventricular arrhythmias or with a poor outcome.\(^17\)

On the contrary, in an extensive post-mortem study among 842 athletes in the USA with autopsy-confirmed cardiovascular diagnoses, male sudden deaths were almost four-times more common than among females, but ACM was more common in females (13% versus 4%).\(^18\) Additionally, total and free testosterone levels were significantly increased in males with malignant arrhythmias compared to males with a favourable outcome, whereas oestradiol was significantly lower in females with malignant arrhythmias compared to females with a favourable outcome.\(^19\) Interestingly, neither ventricular arrhythmias, ACM duration (mean: 6.5±5.6 years), nor heart failure incidence were significantly increased during pregnancy.\(^20\) Finally, the prognostic significance of marked cardiac dilation, reduced deformation, or small patches of delayed gadolinium enhancement in non-symptomatic athletes is unknown; however, cardiac imaging for the assessment of athletes with symptoms, an abnormal ECG, or a positive family history is extremely useful.\(^21\)

**Geographical Origin**

As previously stated, high endurance sports have been associated with sudden death in young athletes and the two most common conditions leading to sudden cardiac death in athletes <25 years old are hypertrophic cardiomyopathy and ACM.\(^22\) Excessive right ventricle wall stress during exercise has also been reported as an inducer of a pro-arrhythmic state resembling ACM.\(^23\) However, there is scarce information about the incidence of ACM in African or Latin American young athletes. Interestingly, non-athletic individuals (n=210) showed evidence of ACM in an African survey,\(^24\) although the authors suggested possible under-registration in low-income countries. On the contrary, in a post-mortem survey with 38 Korean athletes, with a mean age of 27±5 years, ACM was reported in 42% of cases, and no relationship to vigorous physical or competitive activity was observed.\(^25\)

There is a need to address the scarcity of information on ACM incidence in other locations outside Europe, especially in Latin America, because information is principally restricted to Europe, especially Italy, and the USA, with some sporadic reports in Asia and Africa. Sudden death is very often under-represented in countries where healthcare services are deficient, and high endurance athletes are not always assessed after sport practice, making it necessary to establish a survey for pro-arrhythmogenic substrates in young people. Additionally, individuals need to be assessed to identify if genetic factors, such as regional genetic patterns of polymorphisms, are involved in these possible differences.

**Pathophysiology**

**Non-ionic handling related mutations**

Several pathophysiological mechanisms have been suggested for ACM. One of the most cited causes are alterations in the structure and functionality of intercalated discs.\(^26\) It has been reported that desmoglein 2 (DSG2) gene mutations, which code for the desmosomal cadherin desmoglein, cause
ACM affecting cell adhesion, suggesting this is a major pathogenic mechanism in DSG2-related ACM. Additionally, mutated desmin, impairment in filament formation, remodelling of connexin43, and plakophilin-2 mutations have all been reported as possible causes of pathogeny in ACM. Interestingly, the presence of miR-130a-mediated translational suppression of desmocollin and downregulation of connexin43, important proteins in spreading of cell to cell communication, cause cell to cell disturbances, which may be linked to structural degeneration reported in ventricular tissue in ACM patients. Additionally, they can generate a pro-arrhythmogenic substrate for alterations in action potential conduction.

**Ionic or calcium handling disturbances**

Other studies have focussed their attention on ionic signalling disturbance in heart cells. Remodelling of cardiac sodium channels has been proposed as an arrhythmia-inductor in ACM and is associated with changes in Nav1.5, an integral membrane protein and tetrodotoxin-resistant voltage-gated sodium channel subunit. The SCN5a mutation, expression of which is abundant in working myocardium and conduction tissue, has been detected in Chinese patients with ACM, reinforcing suggestions that ion channel dysfunction in arrhythmogenesis plays a role in the onset of ACM. Additionally, intracellular calcium handling through activation of calmodulin dependent protein kinase II and calcineurin A has recently been reported as a novel pathophysiological mechanism, as well as phospholamban-associated R14Del gene mutation and cardiac ryanodine receptor. Phospholamban mutation carriers have ACM characteristics, including important right ventricular involvement, and more often low-voltage ECG, inverted T waves in the left precordial leads, and left ventricular involvement. It is well known that the presence of malignant arrhythmias in ACM patients with non-structural alterations, especially in young people and children, which may be plausibly linked to ionic and calcium handling disturbances, are often associated in other cardiac sudden death causes. Nonetheless, the high variability in clinical and clinical-pathological presentation of ACM makes the analysis of possible causes challenging.

**Possible concomitant causes**

One of the most intriguing issues is the role of inflammation in arrhythmogenic right ventricular cardiomyopathy development, as well as primary and/or secondary causes. Viral infection, alcohol consumption, and autoimmunity are some of the most common causes of chronic cardiomyopathy. The possible role an inflammatory response plays in ACM pathogenesis has not yet been fully addressed, nor the presence of concomitant degenerative heart disease as an inducer of ACM. As such, the next section summarises the findings associated with myocarditis in ACM compared with heart inflammation/degeneration related to other aetiologies.

**EVIDENCE OF INFLAMMATION IN ARRHYTHMOGENIC CARDIOMYOPATHY: INFECTIOUS OR AUTOINMUNE ORIGIN?**

Several reports of autopsied human hearts have suggested the presence of inflammatory infiltrate in subjects diagnosed with ACM. ACM with biventricular involvement was associated with the presence of T cell infiltration in 50% of cases. In another study, scattered foci of lymphocytes with myocardial death were observed in 67% of cases. Patients with fibro-fatty left ventricular involvement observed histologically and macroscopically had inflammatory infiltrates significantly more often than those from patients with isolated right ventricle involvement (73% and 88%, respectively, versus 30%), suggesting an association between global heart affection and inflammation. In concordance with these findings, adipose infiltration of the right ventricle was associated with lymphocytes in 5.5% of cases in a review of autopsies of sudden death. Cytokine disturbance has been described in patients with ACM. Higher levels of pro-inflammatory cytokines patients' interleukin (IL)-1β (1.22±0.07 versus 0.08±0.01 pg/mL; p<0.0001), IL-6 (3.16±0.44 versus 0.38±0.04 pg/mL; p<0.0001), and tumour necrosis factor (TNF)-α (9.16±0.90 versus 0.40±0.06 pg/mL; p<0.0001) in ACM were reported, while levels of the anti-inflammatory cytokine IL-10 were not significantly different (1.36±0.15 versus 1.20±0.30 pg/mL; p=0.74). Interestingly, increased TNF and IL-6 was recently reported in high sudden death risk patients with Chagas disease, an arrhythmogenic infectious cardiomyopathy. Additionally, T-lymphocytes were reported as the main infiltrate cell types in patients with ACM. However, studies assessing the molecular pattern of myocarditis in ACM are scarce and the issue needs to be more deeply addressed.
Concomitant viral infections in ACM have been associated as a cause of inflammation and worsening of ACM outcome. Enteroviral sequences were detected in myocardial samples of seven ACM patients and adenovirus 5 in another two patients from 12 analysed by polymerase chain reaction.\(^4\) Enteroviral RNA with homology to Type B coxsackieviruses was detected in three of 8 ACM patients (37.5%).\(^4\) Other studies, however, failed to find any viral genome in the heart of ACM samples,\(^4\) suggesting multifactorial causes of cardiac pathology. Additionally, several reports have addressed cardiomyocyte apoptosis that may possibly relate to other viral infections. Right ventricle, chamber-specific apoptotic process in ACM patients was reported.\(^4\) In other studies, apoptosis was detected by TUNEL in biopsied heart specimens;\(^5\) endomyocardial biopsies\(^6\) and myocardial damage were closely related to apoptosis in both children and adults.\(^7\) Also, disruptions of the plasma membrane and dissociation of intercellular junctions were associated with discharge of intracellular lipid droplets into the interstitial space,\(^8\) suggesting that apoptosis may be related with desmosome dysfunction. Finally, mRNA for p53, a protein related to apoptosis, was upregulated compared to those with dilated cardiomyopathy and healthy controls.\(^8\)

Other pathogens have also been co-associated to arrhythmogenic cardiomyopathy. Six patients with ACM (12%) had positive (>1:256) immunoglobulin (Ig)G titers in the immunofluorescence test with Bartonella henselae, a proteobacteria that may cause endocarditis in patients with non-ACM familiar antecedents\(^9\) and has been related to sudden death.\(^10\) Additionally, cardiac sarcoidosis arrhythmias have been reported that are similar to ACM and have a high threshold of defibrillation.\(^11\) However, there is very limited information about the functional relationship among viral/bacterial infection, especially if it is possible to establish a direct connection with pathogen invasion or if it is plausible that cellular/humoral autoimmune responses may play a role in ACM pathophysiology.

**Other Arrhythmogenic Pathologies as Potential Cofactors and Models for Assessment of the Role of Inflammation**

Based on the reports analysed here, ACM appears as a complex and multifactorial example of cardiovascular disease. A genetic background may be potentiated by external factors, such as viral infections, which also may explain the wide range of clinical presentations of ACM and the relative early presentation. This issue is of great importance, with the spread of several viruses and protozoan with myocarditis and/or arrhythmogenic potential (Trypanosoma cruzi, Chikungunya, Zika, and Dengue viruses as just a few examples) or autoimmune myocarditis. As such, we considered it important to analyse the reported relationship between cardiac inflammation linked to infection and arrhythmias. It is relevant in two complementary senses: knowing the nature of possible inflammatory substrates, potentially associated with ACM, and improving comprehension of pro-arrhythmogenic mechanisms associated with cardiac inflammatory pathology to explore possible approaches to future research and clarify the role of inflammation in ACM.

**Viral Myocarditis**

Viral myocarditis is becoming increasingly recognised as a contributor to under-reported mortality, and is thought to be a major cause of sudden cardiac death in the first two decades of life.\(^12\) Several viruses, such as Epstein-Barr,\(^13\) hepatitis E,\(^14\) and enterovirus,\(^15\) among others, have been suggested as aetiologic agents of myocarditis. Immune system modulation has a deep impact on evolution of viral myocarditis in different experimental systems. T helper-17 and regulatory T balancing,\(^16\) IL-4 modulation of interferon-γ-mediated T cell response,\(^17\) NF-κB transcription factor,\(^18\) and IL-2 T cell dependent activation\(^19\) have been addressed in the literature, showing the impact of different branches of inflammatory responses in viral myocarditis. Viruses are often pantropic, and this may generate a proinflammatory cardiac milieu and potentially lead to exacerbated cardiac damage. As previously mentioned, information about immune response in ACM is scarce; therefore, cardiac immune response during viral myocarditis may represent a guide for understanding pathogenesis of ACM and to design experimental approaches to study possible inflammatory markers associated to ACM sudden death. Finally, the global spread of non-endemic viruses (Dengue, Zika, and Chikungunya) with cardiac inflammatory potential increases the necessity for full comprehension of comorbidities associated with ACM.

**OTHER ARRHYTHMOGENIC PATHOLOGIES AS POTENTIAL COFACTORS AND MODELS FOR ASSESSMENT OF THE ROLE OF INFLAMMATION**

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Chagas Disease

Chagas disease, caused by intracellular protozoan T. cruzi, is the most important infectious myocarditis worldwide. Initially confined to the American continent, it has begun to spread via immigration to developed countries, mainly to Europe and the USA, representing a comorbidity to ACM to consider. Malignant arrhythmias, often asymptomatic until the fatal final episode, are the principal cause of death in Chagasic patients. Interestingly, a proinflammatory cytokine profile has been associated with high sudden death risk during chronic phases of Chagas disease. Additionally, TNF-blocking agents have shown pro-arrhythmic activity in acute experimental murine models, but in other cases have shown an ability to reduce the correct QT interval, and TNF signalling may be linked with cardiac action potential conduction. IL-17 mediated response has also been shown to play a role in cardiac inflammation during acute Chagasic myocarditis and parasite control, with apparent results about their potential beneficial or detrimental role, which is important considering the deleted role in autoimmune myocarditis models. Thus, the relationship between arrhythmias and myocarditis/sudden death may be an important area to analyze in regard to the role of cytokines and inflammatory infiltrate in cardiac remodelling and/or sudden death in ACM. However, the notable possibility of under-registration of ACM should be considered for the Latin-American population and the possible association between both pathologies.

Autoimmune Myocarditis

Autoimmune myocarditis (AM) is often a consequence of subsequent systemic autoimmune diseases, one of the causes of sudden death in young people. Cardiac involvement during autoimmune and/or auto-inflammatory diseases includes the pericardium, myocardium, endocardium, valvar tissue, and coronary arteries. AM is characterised by sinus tachycardia, QT prolongation, atrioventricular conduction defect, and ventricular arrhythmias and is one of the potential differential diagnosis for ACM.

An interesting aspect of AM that is often ignored is the role of regulatory T immunity in the progression of heart inflammation. Impairment in the thymus negative selection of anti-myosin specific CD4 T cells may have different outcomes depending on the context of antigen presentation to activated T cytotoxic cells. The normal process would be the major histocompatibility complex (MHC) Class II antigen presentation of cardiac myosin by non-activated dendritic cells, leading to T cell anergy or apoptosis induced by regulatory T cells. However, if there are associated proinflammatory stimuli that allow an eventual activation of cardiac resident dendritic cells, the MHC II antigen presentation process would lead to a strong T helper-1 and T helper-17 response and consequent myocarditis. This could plausibly explain the comorbidity observed in AM with different viral infection.

Cytokine, humoral, and cellular responses for AM reflect the inflammatory milieu in the heart. IL-17 is a key factor for understanding autoimmune cardiac inflammation. Retinoic acid receptor-related orphan nuclear receptor γt was upregulated at 21 days post-inoculation of cardiac myosin and IL-17 T cells were recruited at the site of the inflamed heart. In this sense, IL-17A-deficient mice were protected from post myocarditis remodelling and did not develop dilated cardiomyopathy. Additionally, the PKCβ/Erk1/2/NF-κB signalling pathway was related to cardiac fibrosis in AM and neutralisation of IL-17 was able to abolish proinflammatory reaction in a model of viral myocarditis. These findings also highlighted the possible role of IL-6 as a key regulator of shift to T helper-1, 2, and 17.

CONCLUDING REMARKS

Although it seems clear that ACM has a primary genetic origin, the role of possible associated factors is far from being fully understood. It is especially true for inflammation and its possible implications in development of the cardiomyopathy, as well as the possible applications of inflammatory serological markers as auxiliary tools for diagnosis/prognosis. Additionally, the information about ACM incidences in Africa or Latin America need to be expanded to determine if there are regional genetic patterns involved in the pathophysiology of ACM. Inflammation of the myocardium has been identified as a concomitant cause of ACM, with T cells infiltrating patients with biventricular affection; however, the causal effect is not yet well described. Identification of T cell subsets predominant in cardiac infiltrate has proven to be useful in other models of cardiac inflammation/arrhythmias to understand pathophysiology and to propose possible inflammatory markers. In fact, based principally on findings reported to autoimmune or
infectious arrhythmogenic myocarditis, IL-17, TNF, and IL-2 emerge as candidate markers for studying the inflammatory role in ACM. Alternatively, the body of research on viral myocarditis is growing and it has possibly been under-considered in the analysis of pathophysiology of ACM. Viral infections with cardiomyopathic potential are widely distributed and may represent a potential proinflammatory stimulus that can aggravate the outcome of ACM, as have been reported in other kinds of autoimmune myocarditis. The relative scarcity of reports on inflammation in ACM and their potential role in the devastating consequences highlight the particularly urgent need to develop a clear protocol of cardiovascular evaluation for young, high-endurance athletes, including inflammatory biomarkers to prevent fatal episodes of ventricular arrhythmias.

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