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Arrhythmogenic Right Ventricular Cardiomyopathy - what do we know? A review of current knowledge state

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Abstract

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited disorder that is responsible for a considerable number of sudden death cases in young athletes. Its pathological hallmark is a progressive loss of myocytes predominantly in the right ventricle and its simultaneous replacement by fibrous and fat tissue, which in turn leads to an increased risk of potentially lethal ventricular arrhythmias to occur. Over a dozen of mutations have been confirmed as genetic basis of ARVC with most of them affecting genes encoding desmosome proteins, however in up to half of all cases the exact etiology is still unknown. By number of studies, it is implied that physical activity is the most significant environmental factor that impacts the development and course of the disease. The main focus of treatment is to prevent sudden cardiac deaths and additionally to moderate arrhythmic events and heart failure.

Materials and methods: databases including “Pubmed” and “Google Scholar”

Keywords: Arrhythmogenic right ventricular cardiomyopathy, ventricular fibrillation, ventricular tachycardia, implantable cardioverter-defibrillator, sudden cardiac death, heart failure

Abbreviations: ARVC - Arrhythmogenic right ventricular cardiomyopathy, VF - ventricular fibrillation, VT - ventricular tachycardia, ICD - implantable cardioverter defibrillator, SCD - sudden cardiac death, HF - heart failure, nsVT - nonsustained ventricular tachycardia, ARNI - angiotensin receptor-nephtrilysin inhibitor, MRA - mineralocorticoid receptor antagonist, PVC - premature ventricular complex, RV - right ventricle, LV - left ventricle, QOL - quality of life.

Introduction and epidemiology

Initial description of ARVC dates to 1977 with first clinical features of the disease reported in 1982. [1, 2] It is characterized by right ventricular dysfunction, ventricular arrhythmias and sudden cardiac death which are caused by a progressive atrophy and fibrofatty replacement of the right ventricle myocardium. The estimated prevalence in general population is ~ 1:2,000 to 1:5,000 (depending on geographic location) with slight male predominance (55%-60%). [3] The disease is responsible for a significant number of sudden cardiac death cases in young people, especially athletes. According to a meta-analysis by Flavio D'Ascenzi et al. [4] ARVC was a cause of SCD in 11.5% of cases in athletes aged ≤ 35 years (4.7% of cases in non-athletes aged ≤ 35 years) based on 34 different studies between 1990 and 2020.

ARVC is predominantly a disease of the right ventricle, however left-dominant arrhythmogenic cardiomyopathy (ALVC) and biventricular variant also exists. [5, 6]

Etiology

ARVC is inherited predominantly in an autosomal dominant pattern with variable penetrance and expressivity. Up to 50-60% of ARVC cases are caused by mutations of genes encoding desmosome proteins: plakophilin-2 (PKP2), desmoplakin, desmoglein-2, plakoglobin and desmocollin-2, with the most common one being the PKP2 mutation (20%-45% frequency). [7, 9] Another significant mutation affects desmoplakin (DSP) and predisposes carriers to develop left ventricular dysfunction 4-times more likely than PKP2 mutation. DSP mutation carriers are also significantly more likely to experience sudden cardiac death. [8] Mutations in extradesmosomal genes such as those encoding: transforming growth factor B3 (TGFB3), cardiac ryanodine receptor (RyR2), Titin, Catenin Alpha 3 (CTNNA3) have been implicated in specific, atypical forms of ARVC. The genetic cause of ARVC still remains unknown in about 40 to 50% of patients. [9]

Pathogenesis

The entire pathomechanism is not fully understood, however there are number of theories presenting several possible explanations. Current knowledge of genetic background of ARVC indicates that the disease is caused primarily by desmosomal dysfunction. Defective desmosomal proteins may lead to impaired mechanical coupling between individual heart muscle cells. This induces myocytes to detach from one another especially during periods of

increased muscle stress. As a result inflammation occurs, which gradually leads to fibrofatty replacement of the healthy muscle tissue, which in turn, makes heart muscle prone to arrhythmias and in addition causes heart failure at later stages of the disease. This pathogenic model explains why prolonged exercise that elevates heart muscle strain, increases risk of an earlier development of the disease. [10, 11] Due to the fact that the right ventricle has thinner and more distensible wall, this model also explains why right ventricular dysfunction occurs earlier and more often than left one.

Moreover, patients with ARVC have decreased expression of connexin-43 protein, a key component of gap junctions. This is why even in early phases of the disease, where no significant structural defects of the myocardium are present, conduction delays and tachyarrhythmias may transpire. [11]

Clinical presentation and natural history

ARVC usually manifests between second and fifth decade of life. The most common clinical presentation includes syncope, dizziness, palpitations, VT/VF and cardiac arrest. Usually the first symptom is a short syncope caused by a ventricular arrhythmia. However, in up to 10% of the cases SCD or resuscitated cardiac arrest may occur as the first manifestation of the disease in previously asymptomatic individuals (mostly young athletes). [3, 12, 13]

Natural history of ARVC can be divided into four phases. In the first, „concealed” phase there are no significant structural changes in the ventricle yet, but nonetheless, SCD may happen at this stage. In the second phase, aside from the occurrence of ventricular arrhythmias, functional and structural dysfunction of the heart is detectable by imaging tests. Patient may present symptoms such as palpitations, syncope or cardiac arrest. Third phase is characterized by right ventricle failure caused by progressive loss of contractile tissue, with the left ventricle function being relatively preserved. Lastly, in the fourth stage biventricular failure occurs. The disease may resemble dilated cardiomyopathy with its related complications, e.g. atrial fibrillation and thromboembolic events. [12]

Diagnostics

Diagnostic process of a patient with suspected ARVC should start with readily available diagnostic methods such as ECG and echocardiography. Notable abnormalities that may be

present in patients ECG are: QRS duration ≥ 110 ms in V1-V3 leads, S wave duration ≥ 55 ms in V1-V3 leads, T wave inversions in V1-V3 leads, epsilon waves in V1-V3 leads (with epsilon waves being the most specific with the lowest sensitivity) and nonsustained or sustained VT of LBBB morphology with superior axis.

In 24-hour Holter monitoring, result indicative of ARVC is more than 500 PVCs/24h recorded.

In echocardiography: Regional RV akinesia, dyskinesia, aneurysm, RVOT widening are all highly specific findings but with low sensitivity in the early stages of the disease.

If expansion of diagnostics is needed, several options are possible.

An MRI can be performed which can directly show fibrofatty replacement, however, due to the RV wall thinness it is technically difficult to visualize. Moreover, fatty replacement of the myocardium has low specificity to ARVC.

Another diagnostic tool is genetic testing. Number of genes have been identified with the ARVC phenotype, mostly ones that encode desmosomal proteins. Unfortunately, genetic cause remains unknown in up to 50% of patients.

Lastly, a myocardial biopsy may be used to confirm the occurrence of fibrofatty replacement of myocytes in the RV wall. [14]

Role of physical activity

It has been indicated in numeral studies that exercise is the most powerful environmental factor that impacts the development of ARVC and its clinical course. One of the first substantial studies that led to this conclusion was a prospective cohort study by Corrado et al. [15] who reported that young athletes with ARVC had an increased risk of a sudden death comparing to nonathletes with the disorder. Another study by La Gerche et al. [16] found out that high-intensity endurance exercise may induce AVRC phenotype, even in mutation-negative individuals.

Ruwald et al. [17] concluded that patients who participated in competitive exercise had an earlier onset of clinical symptoms and had double the risk of SCD comparing to inactive patients or those practicing recreational sports. In a study by Wang et al. [18] decreased rates of ventricular arrhythmias were ascertained in patients with AVRC who restricted their exercise activity.

Restriction of high-intensity training should be recommended to all ARVC patients, however the potential health benefits of low to moderate levels of physical activity should not be overlooked. Several studies have been conducted to assess the safe threshold of physical

activity for ARVC patients. Sawant et al. [19] examined the safety of the AHA (American Heart Association) minimum exercise recommendations for overall health in healthy desmosomal mutation carriers, which is 450–750 MET (Metabolic equivalent of task)-minutes/week (equivalent of 390-650 MET-hours/year). They concluded that patients who participated in endurance training and higher-intensity exercise yielded worse outcomes, and those who restricted exercise at or below the upper bound of the AHA recommendation, had favorable outcomes with no life-threatening arrhythmias reported. Another study by Segre et al. [20] reported that activity below 700-1100 MET-hours/year is not associated with poor clinical outcomes for gene-positive individuals. Those studies show that low to moderate levels of physical activity may not be detrimental to patient's health and prognosis and they should not be completely deprived of the benefits of exercise.

Treatment

The goal of ARVC management is to reduce mortality and to improve quality of life. As mentioned in the previous paragraph, exercise restriction to a low or moderate level plays a crucial role in preventing disease progression and should be recommended to all ARVC patients. [21]

Pharmacological therapy mostly includes usage of betablockers, antiarrhythmic drugs, and HF drugs. Most commonly used antiarrhythmics are amiodarone and sotalol, which are the most effective with a relatively low proarrhythmic risk. They are recommended in patients with frequent PVCs or/and nsVTs and as an addition to betablockers, when alone they are insufficient to control arrhythmic events in symptomatic patients. [22] If heart failure occurs, the HF treatment includes ARNI, MRA, cardioselective betablockers, flosins and diuretics. In later stages of ARVC, dilation and aneurysms of the ventricles may induce thrombi formation. In case of a documented thrombus or a thromboembolic event, anticoagulant therapy should be implemented. [22]

Patients with ARVC are at high risk of SCD. Implantation of ICD is the main therapeutic option aimed at preventing sudden death, with its efficacy and safety established in numeral studies. [23, 24, 25] The available data indicates that ICD successfully interrupts lethal arrhythmias and improves long-term outcome in selected ARVC patients. One study, in particular, concluded that 48% of patients with primary preventive ICD implantation experienced appropriate ICD interventions over a mean follow-up of 4.7 ± 3.4 years. [25]

Patients who benefit most from ICD are those who have had an episode of VF, sustained VT or have confirmed severe dysfunction of RV, LV or both. In asymptomatic patients with no risk factors (such as: cardiac arrest due to VF/VT, nsVT, moderate to severe ventricular dysfunction, unexplained syncope, compound genotype, male gender) and in healthy gene carriers, there is generally no indication of prophylactic ICD implantation because of the low risk of arrhythmias and the risk of ICD related complications during long-term follow-up. [26]

Ablation is a viable option for treatment that improves patients QOL. It is recommended in cases of frequent sustained VT episodes and recurrent ICD shocks despite maximal pharmacological therapy. It may be also considered in patients who cannot tolerate or do not desire pharmacological therapies. [22] Catheter ablation does not prevent SCD, so it should not be regarded as an alternative to ICD therapy in ARVC patients with a history of sustained VT with the exception of selected cases with a drug refractory, haemodynamically stable, single morphology VT. [23]

Heart transplantation is the final therapeutic option for ARVC patients. The largest assembled cohort of ARVC patients who underwent heart transplant showed high post-transplantation survival rates (94% after 1 year and 88% after a follow-up of 6.2 ± 4.8 years). [27] The procedure is recommended in patients who had early clinical onset of the disease with its progression to an untreatable heart failure or have uncontrollable ventricular tachyarrhythmias which are refractory to ICD therapy and/or ablation.

Conclusions

ARVC is an inherited cardiomyopathy in which impaired function of desmosomes and gap junctions with subsequent fibrous and fatty replacement of myocardium causes potentially lethal ventricular tachyarrhythmias and heart failure in the later stages due to structural dysfunction of the heart muscle. Multiple studies have shown that patients who participate in high-intensity exercise may experience earlier clinical onset and more severe course of the disease and that is why restriction of physical activity is considered to be a paramount resource that prevents ARVC progression. The management of patients is aimed primarily at reducing mortality by ICD implantation combined with pharmaceuticals and ablation which improve QOL with final treatment option for patients with end-stage ARVC being cardiac transplantation.

Author's contribution

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