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Focus on arrhythmogenic right ventricular cardiomyopathy

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KEYWORDS
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Arrhythmogenic right ventricular cardiomyopathy is a myocardial disease generally caused by desmosomal mutations and characterized by progressive replacement of cardiomyocites with fibro-adipose tissue. In the classic form of the disease right ventricle is predominantly affected. However, biventricular and left-dominant variants have been recently recognized, leading to the new nosological definition of arrhythmogenic cardiomyopathy. The condition affects mostly young adults and athletes and is clinically characterized by ventricular arrhythmias, heart failure and sudden cardiac death. The diagnosis is based on clinical-instrumental criteria, including family history, morpho-functional and electrocardiographic abnormalities, ventricular arrhythmias and genetic defects (Task Force Criteria, 2010). The main goal in the management of patients is the prevention of sudden cardiac death, where implantable cardioverter-defibrillator is the only effective therapeutic strategy. Many arrhythmic risk factors have been described. Recently, an on-line calculator has been proposed, but it needs further validation.

DEFINITION

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a primary heart muscle disease, characterized by progressive epi-endocardial replacement of cardiomyocytes with fibro-adipose tissue. Clinically, ARVC is characterized by ventricular arrhythmias, heart failure (HF), and sudden cardiac death (SCD).[1]

The first descriptions of the disease were reported in the '70 s of the last century but only in 1995 ARVC become part of the WHO/IFSC (World Health Organization/International Society and Federation of Cardiology) Classification of Cardiomyopathies.

Originally the disease was known as 'Arrhythmogenic Dysplasia of the Right Ventricle' and was considered as a developmental defect of the right ventricle (RV) myocardium.

Since then, significant progress has been made in knowledge of pathogenetic mechanisms, natural history and clinical management of the disease.

Arrhythmogenic right ventricular cardiomyopathy is caused by a genetic defects, mainly affecting cell junction proteins (desmosomes). Structural alterations may be absent or mild in the initial stages of the disease, confined to a limited regions of the RV, the so called 'triangle of dysplasia'. With the progression of the disease also the left ventricle (LV) may be involved.

Recent researches describe this cardiomyopathy as biventricular, in most cases, also admitting the possibility of a prevalent or exclusive involvement of the LV, known as 'Left-Dominant' variant.[1–6]

Growing evidences of genotypic overlap between ARVC and 'arrhythmic' Dilated Cardiomyopathy (caused by mutations of desmosomal genes, filamin or lamin) led

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to the definition of 'Arrhythmogenic Cardiomyopathy' (AC).[3,5,6]

Arrhythmogenic cardiomyopathy includes a heterogeneous spectrum of phenotypes, ranging from isolated involvement of the RV to exclusive involvement of the LV, sharing a common genetic basis and clinically characterized by electrical instability, that could lead to atrial or ventricular tachyarrhythmias and bradyarrhythmias.

GENETICS

Between 30 and 60% of ARVC/AC cases are familiar and pathogenic mutations are detected in about 60% of cases.[1-3,6]

In the last decades, the spread of Next Generation Sequencing techniques, capable of analyzing enlarged panels of genes in a short time, allowed the identification of the main disease *loci*. Currently 16 genes, whose mutations are responsible for the disease, have been identified.

The most frequently detected pathogenetic mutations affect 5 genes encoding for desmosomes, structures involved in cell-to-cell adhesion.

Placophylline is the most frequently affected protein, along with desmoplakin, desmoglein, desmocollin and plakoglobin.

Besides the mentioned mutations, other genes (i.e. genes encoding for adherent junctions, cytoskeleton components, ion and cytokines channels) have been recognized.

The transmission is mostly autosomal dominant, with incomplete penetrance and variable expression, resulting in a heterogeneous spectrum of clinical manifestations also in the same family.

Less frequently the transmission is autosomal recessive and associated with palmoplantar keratoderma and woolly hair (Naxos and Carvajal syndromes).[1-3]

The genetic test

Genetic test is indicated in subjects with definite clinical diagnosis, in order to identify the mutation responsible for the disease.

If a pathogenic or likely pathogenic variant is found, genetic testing is indicated in first-degree family members, in order to identify at-risk relatives who share the same genetic predisposition of the proband.

First-degree family members could be mutation-carriers, therefore a clinical screening with ECG and echocardiogram starting from 10 to 12 years of age is recommended and, even if negative, must be repeated with individualized timing of re-evaluation.[3,6,7]

Epidemiology

The incidence of the disease is unknown. The prevalence of ARVC in the general population varies in different series between 1:5000 and 1:1000 subjects, with greater prevalence in some geographical areas, such as Veneto Region in Italy.

Male are most affected, with a 3:1 ratio. The onset of disease occurs at young age, between the second and fourth decade, while diagnoses before the age of 12 and after 60 are infrequent.[1,2,4]

Although it is described as a relatively rare disease, ARVC has a significant epidemiological relevance, being one of the main causes of SCD in young adults and athletes.[1-4,8]

CLINICAL EVENTS

In the early stages of ARVC, patients may be completely asymptomatic. In these cases, the diagnosis can be the result of a family screening or an occasional finding.

Even in the absence of symptoms, ventricular arrhythmias (i.e. premature ventricular contractions, non-sustained ventricular tachycardia) can occur, together with major and potentially fatal arrhythmias, mainly during exercise.[1-4,8] The most typical arrhythmias in ARVC have a left bundle branch block morphology, with negative QRS in the right precordial leads and vertical axis on the frontal plane. Ventricular arrhythmias is favoured by the presence of fibro-adipose tissue that alters the normal propagation of the electrical impulse in the myocardium.

Heart failure occurs in less than a third of cases, usually in advanced stages of disease.

Variability of clinical manifestation is related to genetic heterogeneity and variable phenotypic expression. Environmental factors, such as exercise and viral myocarditis, can also play a role in the progression of disease and in the onset of arrhythmias.[1-3]

DIAGNOSIS

The diagnosis is based on clinical and instrumental multiparametric criteria, defined by 2010 Task Force of Experts (*Table 1*), which revised the previous criteria (1994) increasing their sensitivity.[1]

The current diagnostic criteria consider 6 categories, which reflect the main characteristics of the disease: structural and functional abnormalities of the RV, depolarization and repolarization abnormalities on the ECG, arrhythmias, histological tissue characterization, family history and genetics.

Definite diagnosis is made in presence of 2 major criteria, 1 major and 3 minor or 4 minor criteria.

Beside the definite forms of disease, there are also 'borderline' and 'possible' forms, which satisfy a smaller number of diagnostic criteria and are considered as 'minor forms'.

These criteria, although useful diagnostic tool, can only be applied to forms with isolated involvement of the RV. A recent 2019 Consensus Statement[3] confirms and validates these criteria as regards to the diagnosis of ARVC, underlining the lack of defined diagnostic criteria for biventricular or Left-Dominant forms.

Electrocardiographic aspects

The fibro-adipose replacement interferes with the physiological conduction of the electrical impulse in the ventricular myocardium and is the cause of electrocardiographic abnormalities, present in up to 90% of patients.

Table 1. 2010 Diagnostic Criteria of Arrhythmogenic Right Ventricle Cardiomyopathy. Modified from Ref [1].

1. Global and regional dysfunction and structural alterations

Major

Echocardiography

Regional RV akinesia, dyskinesia, or aneurism and 1 of the following (end diastole):
PLAX RVOT $\geq$ 32 mm (corrected for body size PLAX/BSA $\geq$ 19 mm/m^2)
PSAX RVOT $\geq$ 36 mm (corrected for body size PSAX/BSA $\geq$ 21 mm/m^2
or RVFAC $\leq$ 33%

Magnetic Resonance

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
Ratio of RV end-diastolic volume to BSA $\geq$ 110 ml/m^2 (male) or $\geq$ 100 ml/m^2 (female)
or RV ejection fraction $\leq$40%

RV angiography

Regional RV akinesia, dyskinesia or aneurysm

Minor

Echocardiography

Regional RV akinesia or dyskinesia and 1 of the following (end diastole):
PLAX RVOT $\geq$29 to $<$32 mm (corrected for body size PLAX/BSA $\geq$ 16 to $<$ 19 mm/m^2)
PSAX RVOT $\geq$32 to $<$36 mm (corrected for body size PSAX/BSA $\geq$18 to $<$21 mm/m^2
RVFAC $>$33 to $\leq$40%

Magnetic Resonance

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
Ratio of RV end-diastolic volume to BSA $\geq$ 100 to $<$ 110 ml/m^2 (male) or $\geq$ 90 to $<$ 100 ml/m^2 (female)
or RV ejection fraction $>$40 to $\leq$45%

2. Tissue characterization

Major

Endomyocardial biopsy

Residual myocytes $<$60% on morphometric analysis (or $<$50% if estimated), with fibrous replacement of the RV free wall myocardium in $\geq$ 1 sample, with of without fatty replacement of tissue

Minor

Endomyocardial biopsy

Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in $\geq$ 1 sample, with or without fatty replacement of tissue

3. Depolarization abnormalities

Major

Epsilon wave in right precordial leads (V1-V3)

Minor

Late potentials by SAECG in $\geq$1 of 3 parameters in the absence of a QRS duration of $\geq$110 ms on the standard ECG
Filtered QRS duration (fQRS) $\geq$ 114 ms
Duration of terminal QRS $<$ 40 μV (low-amplitude signal duration) $\geq$ 38 ms
Root-mean-square voltage of terminal 40 ms $\leq$ 20 μV
Terminal activation duration of QRS $\geq$ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, V3 in the absence of complete right bundle-branch block

4. Repolarization abnomalies

Major

ECG

Negative Twaves in right precordial leads or beyond in individuals $>$ 14 years of age (in the absence of complete right bundle-branch block QRS $\geq$ 120 ms)

Minor

ECG

Inverted Twaves in leads V1 and V2 in individuals $>$ 14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6
Inverted Twaves in leads V1, V2, V3, and V4 in individuals $>$ 14 years of age in the presence of complete right bundle-branch block

5. Ventricular arrhythmias

Major

Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis

Minor

Non-sustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis or unknown axis
At least 500 ventricular extrasystoles per day at Holter

(continued)

6. Family history and genetics

Major

Definitive diagnosis of ARVC in a first-degree family member (Task Force 2010)

Autoptic diagnosis (or from transplanted heart analysis) of ARVC in a first-degree family member

Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation

Minor

History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria

Premature sudden death (35 years of age) due to suspected ARVC/D in a first-degree relative

ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX RVOT = parasternal long-axis right ventricle outflow tract, PSAX = parasternal short-axis, RVFAC = right ventricle fractional area change, RV = right ventricle, SAECG = signal-averaged ECG.

Electrocardiographic alterations often precede structural abnormalities and symptoms. Both depolarization and repolarization can be affected.

The most frequently described finding is the inversion of Twaves in the precordial leads (V1-V3) in absence of a right bundle branch block, due to the structural alterations of the RV. If LV is involved, the same repolarization abnormalities can also extend to the inferior and/or lateral leads. A complete or incomplete right bundle branch block is common.

Characteristics of the ARVC, although less frequent, are epsilon waves, defined as reproducible low-amplitude signals between the end of QRS complex and the onset of the Twave.

Other abnormalities (i.e. QRS elongation, prolonged 'upstroke' of the S wave in the right leads, low voltages, QRS fragmentation) can be found, and can be considered as markers of advanced disease.[2,3]

Imaging

The assessment of volumes, kinetics and ventricular function can be performed with different imaging modalities such as echocardiography, angiography, magnetic resonance (MR), and computed tomography.[1-3,9-12]

Although MR represents the gold standard for the evaluation, echocardiogram is often performed firstly, being more accessible and less expensive. Echocardiography has some known limits, especially for the study of the RV, characterized by complex anatomy and function. Suggestive findings include ventricular dilation and dysfunction, regional kinetic abnormalities and aneurysms.

To date, non-invasive tissue characterization is not included in the diagnostic criteria, although an improvement in diagnostic accuracy through its use has been described.[1,11] Fat and fibrosis detected by MR corroborates the ARVC diagnosis and represents a useful tool for prognostic stratification.[2,3,11]

The spread of the MR imaging has also increased awareness of frequent left ventricular involvement.

Deformation imaging by echocardiography or MR are not yet included in clinical practice. However, evidences from literature suggest that myocardial strain is able to identify early myocardial involvement in subclinical forms of the disease.[9]

Initial evaluation and follow-up

The initial evaluation includes an accurate individual and familiar history, clinical examination, first/second level examinations (12-lead ECG, signal-averaged ECG, 24-hour Holter-ECG, stress test and transthoracic echocardiogram) and third level exams, such as cardiac MR.

Invasive investigations (i.e. RV angiography and endomyocardial biopsy) are not routinely performed and reserved for selected cases.

A regular follow-up is necessary, with a variable frequency according to individual clinical needs (usually annually), in order to monitor the progression of the disease, assess symptoms, and periodically re-stratify the arrhythmic risk.[3,6,12-14]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ARVC includes conditions such as Idiopathic Ventricular Tachycardia originating from the right ventricular outflow tract, commonly found in young people and not associated with structural disease; Dilated Cardiomyopathy, that shares genotypic and phenotypic elements in overlap with ARVC; Sarcoidosis and Myocarditis, in which MR imaging plays a fundamental role for the diagnosis; channelopathies; congenital conditions with right ventricular involvement (Uhl's disease, Fallot's Tetralogy).

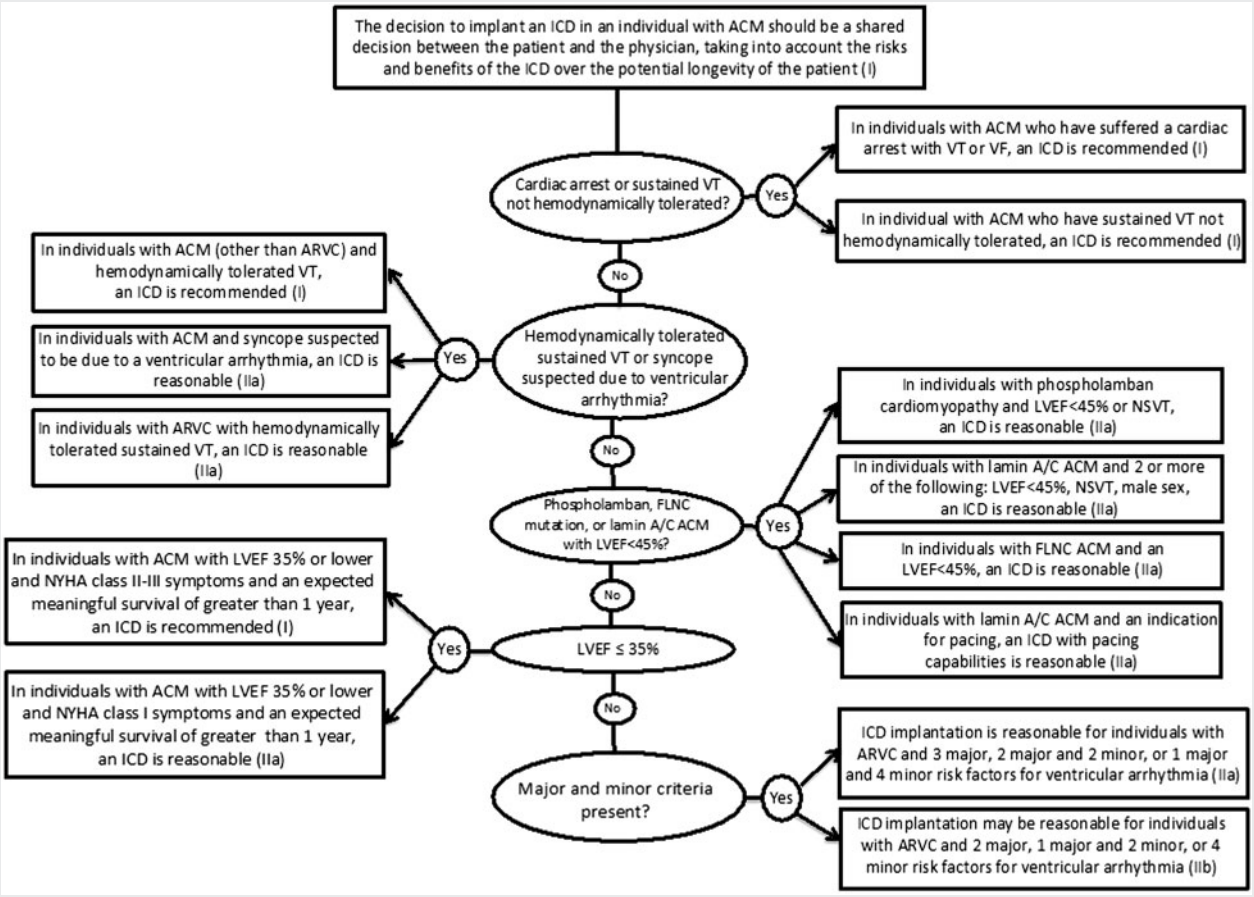
ARRYTHMIC RISK

The main goal in the management of ARVC patients is the correct arrhythmic risk stratification.

Although the implantable cardioverter-defibrillator (ICD) has proven to be an effective tool in preventing SCD, it is not a strategy without short and long-term complications (device infections, inappropriate shocks, malfunction, psychological as well as life style impact). Therefore, it is necessary to carefully evaluate the indications for the implantation according to patient's risk.[2,3,12-16]

Patients who have already experienced a major arrhythmic event (sustained ventricular tachycardia, ventricular fibrillation) have a class I indication to be protected with ICD.[3]

Table 2. Recommendations for an implantable cardioverter-defibrillator. Modified from Ref [3].



ICD = implantable cardioverter-defibrillator; ACM = Arrhythmogenic Cardiomyopathy; VT = Ventricular Tachycardia; VF = Ventricular Fibrillation; LVEF = Left Ventricular Ejection Fraction; ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy; FLNC = Filamin-C; NYHA = New York Heart Association.

The debate is still open regarding the primary prevention of sudden death in those who have never experienced potentially fatal ventricular arrhythmias.

In order to correctly stratify their arrhythmic risk, the most recent 2019 Expert Consensus document [3] (*Table 2*) suggests considering the presence of some major criteria (i.e. non-sustained ventricular tachycardia, inducibility of ventricular tachycardia during the electrophysiological study, ejection fraction of the LV <49%) and minors criteria (male sex, proband status, >1000 premature ventricular contractions in 24 hours, right ventricular dysfunction, presence of 2 or more desmosomal mutations). Implantable cardioverter-defibrillator implantation should be considered especially in patients with 3 major, 2 major and 2 minor or 1 major and 4 minor arrhythmic risk criteria.

In the overall risk assessment it is necessary to consider the presence of highly arrhythmogenic mutations (i.e. lamin, filamin C and phospholamban).

Recently, Cadrin-Tourigny *et al*. proposed a new predictive model of sustained ventricular arrhythmias, whose risk of onset at 1, 2 and 5 years can be calculated with a score (www.arvcrisk.com) .[16]

Although this proposal introduces an element of innovation, the score has some limitations, being applicable only at the time of diagnosis and only to the forms of disease that meet the Task Force Criteria 2010.[1] Furthermore, some important elements in the evaluation of arrhythmic risk, such as the presence of tissue abnormalities on MR and genetic mutations, are not considered by the calculator.[3]

ROLE OF PHARMACOLOGICAL THERAPY

The purpose of drug therapy in patients with ARVC is to control arrhythmias and related symptoms, and to treat heart failure when indicated. At the present time, randomized trials on the use of drugs are not available, however, the experiences of international registries suggest that beta-blocker therapy, especially with Sotalol, and the use of Amiodarone in selected cases, are the most effective

strategies. A possible role in the prevention of SCD has not yet been proven. These drugs are also used to reduce inappropriate shocks in ICD carriers.[2,3]

In patients presenting with HF, it is appropriate to start the anti-neurohormonal therapy as suggested by international recommendations.[3]

TRANSCATHETER ABLATION

Transcatheter ablation is an effective tool that may be consider to reduce episodes of recurrent monomorphic ventricular tachycardia and ICD shocks in patients who do not respond to medical therapy or if it is contraindicated. Considered the pathological substrate of the disease (fibro-adipose replacement from the epicardium towards the endocardium), the conventional endocardial approach may be integrated with an epicardial approach.[2,3]

CARDIAC TRANSPLANTATION

In rare, selected, cases there may be a need for heart transplantation due to refractory HF, while incessant ventricular arrhythmias are an infrequent indication.

PHYSICAL ACTIVITY: ROLE IN THE PROGRESSION OF DISEASE AND SUDDEN DEATH RISK

According to some series, ARVC is the main cause of SCD in athletes in Italy.

Physical activity is believed to promote disease progression, development of ventricular dysfunction and adrenergic stimulation that can trigger malignant arrhythmias in patients with favourable pathological substrate.[1–4,8,14]

Athletes affected by AC die mainly during exertion and have a risk of sudden death 2 to 5 times higher in comparison with non athletes.

For this reason, competitive sports are contraindicated in patients diagnosed with ARVC.[2,3]

Furthermore, it is appropriate to illustrate the risks associated with sports, especially of endurance, to genotype-positive subjects, even if presenting a negative phenotype.

FUTURE PROSPECTIVES

We hope the progress of knowledge will allow to act on the underlying molecular and genetic mechanisms, leading to a definitive cure.

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