REVIEW

Arrhythmogenic right ventricular cardiomyopathy/dysplasia

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Abstract

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a progressive disease of predominantly right ventricle, characterized by ventricular arrhythmias possible leading to sudden cardiac death. Genetic predisposition was confirmed more than 15 years ago. Autosomal dominant are forms ARVD1-9, Naxos disease (with subtype Carvajal syndrome) is recessive.
In ARVC/D forms associated with desmosomal disorders are ventricular arrhythmias caused by the presence of myocardial damage and in forms associated with ryanodine receptor mutation is electrical instability and subsequent myocardial damage caused by calcium cell overload.
Main clinical signs are ventricular arrhythmias originated from areas with slow conduction. Progression of ARVC/D is manifested by RV dilatation and LV echocardiographic abnormalities both considered as main risk factors of fatal ventricular arrhythmias and sudden cardiac death.
Therapeutic possibilities include antiarrhythmic drugs, catheter ablation and implantation of cardioverter-defibrillator, in severe right or both ventricle involvement even heart failure treatment *(Tab. 1, Ref. 56).*
Key words: arrhythmogenic right ventricular cardiomyopathy, arrhythmia.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a progressive disease of predominantly right ventricle, characterized by ventricular arrhythmias possible leading to sudden cardiac death.

Since 1996 it is classified as cardiomyopathy (1) with fibrofatty infiltration of right ventricle. Initially, infiltration is regional, later global one and affecting left ventricle with relative sparing of the septum (2). At present, infiltration is viewed as a healing process (3) due to programmed cell death – apoptosis (4). In Slovakia, ARVC/D was first described in 1997 (5).

Genetic predisposition

Genetic predisposition was confirmed more than 15 years ago (6).

Autosomal dominant are forms ARVD1-9, Naxos diasease (with subtype Carvajal syndrome) is recessive.

Loci for ARVD1, ARVD2 and ARVD 4 were first described by Rampazzo (7, 8, 9), locus for ARVD3 described Severini (10). Later loci for ARVD5 and ARVD6 were described (11). Melberg (12) found locus for ARVD7, Rampazzo (13) for ARVD8 and Coonar (14) found locus for Naxos disease.

Presented are characteristics of individual ARVC/D forms, loci and products of known gene mutations (Tab. 1).

In ARVD1 a mutation of transforming growth factor (TGF) beta3 was found (15). TGF beta3 is a member of TGF superfamily. In most cells it inhibits proliferation and induces epithelial apoptosis. On contrary, it stimulates mesenchymal cells proliferation and extracellular matrix production and fibrotic response in vivo (16).

In ARVD2 a mutation of gene encoding cardiac type 2 ryanodine receptor was found (17). Characteristic are polymorphic, exercise-induced arrhythmias. Cardiac ryanodine receptor plays an important role in intracellular calcium homeostasis and cardiomyocytes excitation and contraction coupling. In this case a failure of calcium channels to remain closed is proposed. Thus and intensive adrenergic stimulation leads to intracellular calcium overload, triggering severe arrhythmias (17, 18).

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An unknown mutation in ARVD5 leads to high mortality (19).

In dominant ARVD8 form a mutation of a gene encoding desmoplakin was found (13). Desmoplakin is the most abundant component of desmosomes and together with plakoglobin anchors to desmosomal kadherins, forming a net of non-transmembrane proteins connected to keratine intermediane filaments (20).

ARVD9 is characterized by mutation of plakophilin-2, essential protein of cardiac desmosomes. This mutation may alter intercellular contacts and disrupt cardiomyocytes junctions, in particular as a reaction to mechanical stress (21).

Recessive form Naxos disease was first described in 1986 (22) at Greek isle of Naxos. In this form, cardiomyopathy is accompanied with characteristic phenotype: woolly hair and palmoplantar keratodermia. Mutation of a gene encoding plakoglobin was described by McKoy (23). Plakoglobin is the key component of desmosomes and adherent cell junctions, the only known component with signaling function (24).

Carvajal syndrome, subtype of Naxos disease, is characterized by homozygous mutation of desmoplakin, in contrast to ARVD8. This form is associated with palmoplantar keratodermia and wooly hair with dominant left ventricle involvement (25); described in Ecuador (26).

Since in ARVD/C mutation of plakoglobin, desmoplakin and plakophilin were described it is possible to consider this disorder as a "disease of desmosomes" (27). Mutations in genes coding desmoplakin and plakoglobin indicate, that disorders of cell junction integrity might lead to myocytes death and fibrofatty infiltration healing process. Mutations of gene coding cardiac ryanodine receptor suggest that cytoplasmatic calcium cell overload might lead to arrhythmias (28). It may be concluded that in ARVC/D forms associated with desmosomal disorders are ventricular arrhythmias caused by the presence of myocardial damage and in forms associated with ryanodine receptor mutation is electrical instability and subsequent myocardial damage caused by calcium cell overload (29).

Currently known gene mutations were identified in 40 % of patients with ARVC/D, therefore another causal, yet not observed mutations exist (29).

Clinical characteristics

Exact incidence and prevalence is not known. ARVC/D markedly contributes to sudden death of young people. Both genders are equally affected with the highest risk in fourth life decade (30).

From the anatomic point of view, infiltration affects epicardium and mid-myocardium, with relative sparing of endocardium (31, 32). Fibro-fatty infiltration is found in segments with residual myocytes interspersed between adipocytes and fibrous tissue, creating a substrate for reentry arrhythmias (33, 3).

Thiene (34) described two variants of ARVC/D: lipomatous form and fibro-lipomatous form. In lipomatous form, transmural infiltration is present and wall thickness might be increased. Small areas of fibrous tissue are hard to recognize. This form is usually restricted to right ventricle. In fibro-lipomatous form,

Tab. 1. Characteristics of Individual ARVC/D forms.

Form	Locus	Product of gene mutation
ARVD1	14q24.3	TGF beta3
ARVD2	1q42–q43	ryanodine receptor
ARVD3	14q12–q22	
ARVD4	2q32.1–q32.3	
ARVD5	3p23	
ARVD6	10p12–p14	
ARVD7	10q22.3	
ARVD8	6p24	desmoplakin
ARVD9		plakophilin
Naxos disease	17q21	plakoglobin
(Carvajal syndrome	6p24	desmoplakin)

the wall is thin and aneurysms might be present. Left ventricle (LV) is affected in half cases. Fatty infiltration alone is not adequate for establishing a diagnosis of ARVC/D (35). It is necessary to detect a significant fibrosis in fibro-lipomatous form and degenerative changes in lipomatous form (36).

Structural abnormalities include dilatation, diffuse hypokinesis or regional abnormalities of wall movement with possible aneurysm formation. Contrast ventriculography is the most reliable procedure for evaluating structural abnormalities (32). Almost selective right ventricle affection may be related to higher extensibility of right ventricle free wall compared to left ventricle (13).

Affected proteins in cardiac desmosomes might impair intercellular contacts and affect the response of ventricular myocardium to mechanical stress. These changes might be present predominantly in areas with high stress, like right ventricle outflow tract, apex and sub-trikuspidal areas, known as "the triangle of dysplasia" (27). It is known that it is the stress of cardiomyocytes which modulates the process of elementary calcium release from ryanodine receptors (37).

In ARVC/D patients, apoptosis (4) and inflammatory infiltrates (lymphocytes) (33, 38) suggesting focal myocarditis were observed. Focal myocarditis might explain sporadic cases of this disease (32). Cardiotropic viruses (enteroviruses and adenoviruses/ are more frequently observed in ARVC/D patients compared to control subjects. Their role is unclear, they can contribute to pathology or the affected myocardium might be more susceptible to viral infection.

Electrocardiographic changes include inverted T waves in precordial leads and right ventricle late potentials seen as epsilon waves during standard ECG. For better identification of epsilon waves it is recommended to record ECG with double amplitude at paper speed 50mm/sec, using a 40 Hz filer (39). Inverted T waves in precordial leads beyond V1 were observed in 54 %, epsilon waves in 23–75 % and QRS in V1–V3 longer than in V4–V6 in 98 % (40).

Main clinical signs are ventricular arrhythmias originated from areas with slow conduction. They manifest like palpitations, extrasystoles or sustained ventricular tachycardia (VT) mostly from right ventricle (RV) and sudden cardiac death. To

establish a diagnosis, following combination of history, ECG, arrhythmia and structural criteria is important

Family history

Major: family disease confirmed by biopsy or necropsy.

Minor: premature sudden death (<35 years) suspected from ARVC/D family disease (clinical diagnosis).

ECG conduction/depolarization abnormalities

Major: epsilon waves or localized QRS prolongation (>110 ms) in precordial leads (V1–V2).

Minor: late potentials on signal averaged ECG.

ECG repolarization abnormalities

Minor: inverted T waves in precordial leads (V2–V3) in people more than 12 years old without RBBB.

Arrhythmias

Major: sustained or nonsustained VT with LBBB morphology recorded by ECG, Holter monitoring or during electrophysiologic study,

frequent ventricle extrasystoles (>1000/24 hour during Holter monitoring).

Global or regional dysfunction or structural abnormalities (shown by echocardiography or ventriculography)

Major: severe dilatation and decreased RV ejection fraction without or with mild LV affection

localized RV aneurysms, severe segmental RV dilatation.

Minor: Mild global RV dilatation or decreased RV ejection fraction with normal LV,

mild segmental RV dilatation, regional RV hypokinesis.

Tissue wall characteristic

Major: fibro-fatty infiltration on endomyocardial biopsy.

Patients must fulfill 2 major or 1 major and 2 minor or 4 minor criteria (2, 41).

Standard criteria should be adjusted in relatives of ARVC/D patients. It is possible to establish a diagnosis if inverted T wave in precordial leads, late potentials, VT with LBBB morphology or mild echocardiographic abnormality are present (42).

Ventricular tachycardia is usually easy inducible during electrophysiological study. Corrado (43) found 88 % and Wichter (44) 72 % rate of inducibility.

Endomyocardial biopsy may improve a diagnostic accuracy in ARVC/D due to characteristic topographic and histological features (2). Thus it is recommended to take sample from RV free wall with the risk of perforation (45) or from the connection of septum and free wall (46). In vivo histologic diagnosis of ARVC/D is based on certain amount of fibrous and/or fatty tissue: atrophic myocard with residual myocytes less than 45 %, fibrous tissue more than 40 % and fatty tissue more than 3 %.

Sensitivity and specificity of these markers is 67 % or 92 %, respectively (47).

ARVC/D classification based on clinical findings was first described in 1998 (48). In differential diagnosis it is important to consider "right ventricle cardiomyopathies", mainly Uhl`s anomaly, RVOT tachycardia and Brugada syndrome (49).

Progression of ARVC/D is manifested by RV dilatation and LV echocardiographic abnormalities both considered as main risk factors of fatal ventricular arrhythmias and sudden cardiac death (50). Restricted data on risk stratification suggest that patients with severe RV dysfunction, LV involvement and history of syncope or cardiac arrest are more prone to life-threatening VT and sudden death (51).

Concurrent presence of right and left ventricular abnormalities might be described as biventricular dysplasia (52). Biventricular failure (with disproportional RV affection) might mimic dilated cardiomyopathy (50).

Therapy

ARVC/D is not a benign disease and requires long term individual and effective treatment reducing clinical symptoms and preventing sudden cardiac death. Therapeutic possibilities include antiarrhythmic drugs, catheter ablation and implantation of cardioverter-defibrillator (ICD) (51), in severe right or both ventricle involvement even heart failure treatment (41).

ARVC/D patients without history of syncope or cardiac arrest, premature ventricular beats, cuplets or short runs of VT do not require specific antiarrhythmic therapy. Antiarrhythmic drugs are aimed to decrease VT recurrence and prevent sudden cardiac death.

At present no prospective and randomized clinical studies aimed to antiarrhythmic drug efficacy in ARVC/D patients are available (51).

The most experienced short and long term drug efficacy was published in 1992 (53). The study, involving 191 patients identified sotalol as the most effective antiarrhythmic drug with a total efficacy rate of 68 %. Similar antiarrhythmic profile was observed using a combination of amiodaron and beta-blockers.

In radiofrequent catheter ablation, an acute success was observed in 60–80 % of cases, but VT recurrence was present in 50–70 % of cases during 3–5 year follow up. At present, indications for radiofrequent catheter ablation include patients with localized form and monomorfic, well tolerated VT (curative approach) or patients with frequent recurrence of VT refractory to drug treatment and patients with frequent therapeutic ICD discharges (paliative approach) (51).

ICD implantation is increasingly used for both primary and secondary sudden death prevention in ARVC/D patients. Up till now, no prospective randomized clinical studies compared ICD with drug therapy or catheter ablation. Several studies evaluated ICD efficacy in ARVC/D patients (19, 43, 44). During the first year after implantation was an adequate therapeutic ICD discharge recorded in most patients. This therapy was probably life saving in relevant portion of patients. It might be suggested that ICD

therapy improves long term prognosis and survival in ARVC/D patients when selectively applied to a high risk population (51).

With ICD implantation a low risk of associated complications is reported. Myocardial atrophy progression and fibro-fatty substitution in site of implantation may lead to the loss of sensory function and necessary exchange or replacement of the lead (51). Accepted indications for ICD therapy in ARVC/D patients include secondary prevention after cardiac arrest and/or sustained VT (54).

An ongoing European multicentric register (55) and North America register (56) will provide an important data on risk stratification and treatment efficacy, which might adjust therapeutic strategies and thus improve long term prognosis in ARVC/D patients.

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