Review article

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ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY, NAXOS ISLAND DISEASE AND CARVAJAL SYNDROME

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The aim of this article is to present arrhythmogenic right ventricular cardiomyopathy (ARVC) and the associated cardiocutaneous syndromes, Naxos and Carvajal, with extension on the left ventricle and a new mutation of the desmoplakin gene. ARVC is an inherited cardiomyopathy characterized by myocyte necrosis, dominantly in the right ventricle. It is a significant cause of sudden death in children and adolescents. A thorough family history and modern diagnostic and treatment approach are prerequisites for prevention of sudden death syndrome. Diagnosis is more often established in adults than in children. Within ARVC there are two entity forms, referred to as the Naxos syndrome and the Carvajal syndrome. If ARVC also has palmoplantar keratoderma with distinctive hair features (woolly hair), it is described as Naxos syndrome, but if cardiomyopathy is spread over both ventricles, with even more severe changes on the left ventricle, the entity is referred to as Carvajal syndrome. Inheritance is autosomal recessive, and the mutation is in the desmoplakin gene. Genetic heterogeneity is less pronounced than in the Naxos syndrome. Typically, the disease mostly attacks the left ventricle. **Conclusion** – In order to prevent sudden cardiac death in children, it is important to recognize the special criteria for ARVC in children, published in 2010. These state the spectrum of phenotypic expressions with the primary changes to the right ventricle, but with the spread of cardiomyopathy to the left ventricle (Carvajal syndrome), and cardiocutaneous changes (Naxos syndrome).

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterised by atrophy and necrosis of the myocardium myocytes in the right ventricle and their replacement with connective and often fatty tissue. Clinically, the process is initially characterized by occurrence of life-threatening arrhythmias, gradually leading to failure of the ventricles. The disease was described as a separate entity in the early 1980's (1, 2, 3). The term "dysplasia" originated at a time when it was thought that the disease was caused by a defect in the differentiation and development of the right ventricle, and that it had no genetic basis. Today the majority finds the term "cardiomyopathy" more correct, in fact the issue at hand is primary ("sui generis") cardiomyopathy. Prevalence of the disease in the general population is 1:2000 to 1:5000 (4, 5, 6). It is three times more frequent in males. A family inheritance pattern is found in 30 to 50% of patients (4, 7). Unfortunately, in many cases the first mani-

festation of the disease is malignant arrhythmia, so it is a very common cause of death in young athletes (11-22% of sudden deaths of athletes) (7, 8).

The aim of this article is to present arrhythmogenic right ventricular cardiomyopathy, and the associated cardiocutaneous syndromes, Naxos and Carvajal. A particular purpose is to highlight the new criteria for diagnosis of ARVC in children (published 2010.) and present the new mutation of the desmoplakin gene in our patient with Carvajal syndrome (the spread of cardiomyopathy to the left ventricle).

Etiology and pathogenesis

The disease is genetically determined, with very different phenotypes - clinical manifestations. Genetic diversity is such that there are also ethnic differences. For example, malignant arrhythmias seem to be more common in Italians than in Chinese (8). In most cases the disease is autosomal and dominantly inherited, with the exception of two autosomal-recessive genetic syndromes – Naxos (JUP gene mutation) and Carvajal (DSP gene mutation), where ARVC is combined with skin and hair alterations, and is characterized by a severe clinical finding and early involvement of the left ventricle, with different degrees of penetration and variable expression. These two syndromes have a peculiar clinical finding, so they are described separately at the end of this text (9). However, in some cases the underlying genetics are not clear. The expression of the disease is also thought to depend somewhat on external factors: particularly burdening the heart (e.g. strenuous sporting activity), possibly also viral infection. The first locus was identified in 1994 in a family from Venice. Today twelve genotypes are known, and some authors mention thirteen. The most common is ARVC9 (11-43% of patients) (8, 10).

The pathogenesis is connected with desmosomes, so the disease is sometimes referred to as desmopathy. Desmosomes also take part in the cell-to-cell transfer of electrical impulses, and are in a way responsible for cellular mechanical linkage. The issue in all ARVC cases is alterations in the gene coding of the desmosomal proteins. Parts of the protein structure, particularly the mutated part, are in the part of the desmosomal complex located inside the cell: desmoplakin and plakoglobin. Specifically, gene mutation that takes place in the common genotype ARVC mentioned is a mutation of the gene for plakofilin-2 (PKP2), a protein important for connecting extracellular parts of a desmosome with its intracytoplasmatic parts. Therefore, it is cytosceletopathy. Mutations of genes not directly in charge of the desmosome protein synthesis are very rare, but they probably participate in its function in some way. Be that as it may, ARVC is a disease of intercellular linkage: desmosomes break and the loss of mechanical and "electrical" intercellular links occurs. This leads to cell separation and, in a yet insufficiently explained way, this encourages inflammatory – and particularly – fibrotic reactions. Desmosomal proteins have a double role: as structural proteins in intercellular links, and as signal molecules, the molecules which can alter signal routes and gene expression, promote apoptosis and intercede the expression of fibrogenic and/or adipogenic phenotypes (10). In experiments on mice, it was shown that mechanical (volume) heart overload speeds up the process, and this is certainly also the case in humans (8, 9, 10).

Histological finding

Histologically, the myocardia contains connective, and often fatty infiltrations, with areas of surviving myocites (which later cause extrasystoles, impulse circling and tachycar-

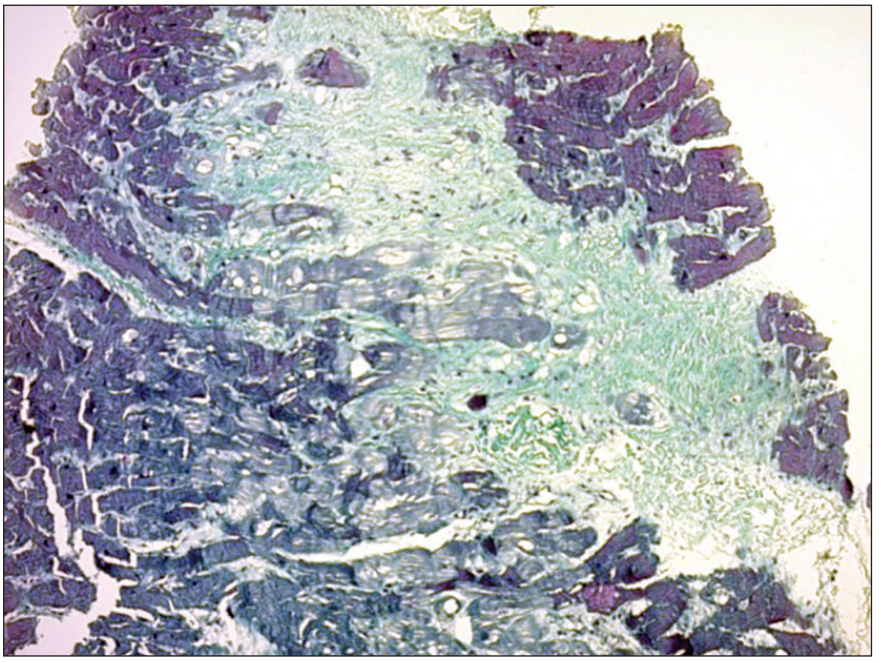

Fig. 1 *Histological section of right ventricular muscle. There is marked dense interstitial fibrosis, within which are embedded isolated myocardial fibres. Cellular connective tissue gradually transforms into a sclerotic acellular scar, (× 100, Mallory stain; from our own archives).*

dia). The presence of fatty cells in the myocardia is not pathognomonic, so the evaluation of a finding should also consider other histological changes as well as the clinical finding. The process of exchanging the myocardia cells with connective and fatty tissue starts subepicardially and spreads towards the endocardium. It is most emphasized in the "triangle of dysplasia" comprised of the inferoapical region and right ventricle infundibulum. Sometimes aneurysmal expansions occur. The process may also be more diffuse (Fig. 1). Initially only the right ventricle is affected, and in the further development in 70% of cases the left ventricle is also affected. Then the symptoms are more serious, with pronounced cardiomegaly, possible mitral or tricuspid valve prolapse, more frequent arrhythmias and heart failure. It seems that there is no connection between Uhl's anomaly (no myocardia in the right ventricle) and ARVC (8).

So far the proportion of children in clinical trials has been relatively small (11, 12, 13). In a large group of 416 patients diagnosed as the first family members with ARVC, all were diagnosed after the age of 10, but only thirteen before the age of 13. (11). However, in the original study by Thiene et al. (14), which describes ARVC as a cause of death in the young, as many as 50% of the deceased were children and adolescents, with sudden death often being the first sign of the disease. There are sporadic reports of ARVC clinical findings in infants and young children, usually with both ventricles affected (14, 15, 16, 17).

Clinical finding

Although the etiopathogenesis of the disease is, as mentioned, peculiar, it is usually first manifested by a cardiac arrhythmia, which may also be lethal. For this reason, early diagnosis is essential for patients. Although the

disease certainly exists from birth, with the symptoms most commonly starting in adolescence, diagnoses have so far generally been made in adulthood, unfortunately too often during autopsies. Clinical findings are also influenced by the diverse penetration (expression), so the clinical symptoms vary accordingly. Initially, the most usual symptoms are palpitations or atypical chest pains, and a syncope in about a quarter to a third of patients. The same proportion of patients have sudden cardiac death as the first symptom of the disease, and in about a quarter of patients the first symptom is symptomatic permanent ventricular tachycardia (VT) (1). The typical arrhythmia is monomorphic ventricular tachycardia, which may be permanent or transitory. Tachycardia is often connected with physical effort or may occur immediately after effort. This is why sudden deaths occur more often in athletes. In the advanced stages signs of cardiac failure appear – almost as a rule (yet with exceptions!) starting with the right ventricle, and then both ventricles. In its final stage the disease resembles dilated cardiomyopathy.

It may generally be said that ARVC has four phases: 1) the asymptomatic phase; 2) manifest electrical disturbances, 3) right ventricle failure, 4) bilateral ventricle failure. It seems that the course of the disease does not depend solely on the underlying genetics, but also on external factors (e.g. mechanical cardiac overload) (18, 19, 20). In some patients extra-cardiac manifestations of typical skin and hair alterations occur. Two such cardiocutaneous syndromes are distinguished: Naxos island disease and Carvajal syndrome (see description in the appendix of this manuscript).

Diagnosis

Timely diagnosis is extremely important for implementing a prevention strategy which would avert an unfavorable outcome for the patient. In so doing, in the advanced stages of the disease it is important not to mistake ARVC for other cardiomyopathies, particularly dilated cardiomyopathy or sarcoidosis (extra-cardiac alterations!).

ESC Working Group criteria

Since an ARVC diagnosis is not simple and it includes combining multiple information sources (picture methods, biopsy, ECG, etc.), the European Society of Cardiology Working Group has devised diagnosis criteria. The first criteria were published in 1994 with the idea of helping cardiologists not to mistake ARVC for dilated cardiomyopathy or idiopathic right ventricular outflow tract tachycardia. Although they were highly specific, these diagnostic criteria were not sensitive enough for the early stages of the disease, or for mild clinical findings, and were particularly useless for screening within affected families. Since new diagnostic methods and findings have surfaced in the meantime, in 2010 the Working Group published revised criteria (21) (Table 1).

This time they took into consideration the significantly higher likelihood of subtle ECG or echocardiography changes being linked with ARVC in family members of ARVC patients. The advancement of diagnostic methods (particularly MR technology development) will soon require the criteria to be updated. Table 1 shows the current (revised) Working Group guidelines. Diagnosis is “definitive” if two of the major criteria are present, OR one major and two minor, OR four minor criteria from different categories. “Borderline” confirmation of the disease is confirmed if one major and one minor criterion are present, OR three minor criteria from different categories. The disease is “possible” if one major OR two minor criteria from different categories are present.

Table 1 Revised Task Force 2010 Criteria (21)

Major	Minor
I. Global or regional dysfunction and structural alterations	
By 2D ECHO	
Regional RV akinesia, dyskinesia or aneurysm and 1 of the following (end diastole): • PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) • PSAX RVOT ≥3 mm ([PSAX/BSA] ≥21mm/m^2) • or fractional area change ≤33%	Regional RV akinesia or Dyskinesia and 1 of the following (end diastole): • PLAX RVOT ≥29 to <32 mm ([PLAX/BSA] ≥16 to <19 mm/m^2) • PSAX RVOT ≥3 mm ([PSAX/BSA] ≥18 to <21 mm/m^2) • or fractional area change >33% to ≤40%
By MRI	
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following (end diastole): • Ratio of RV end-diastolic volume to BSA ≥110 ml/ m^2 (male) or ≥100 ml/ m^2 (female) • Or RV ejection fraction ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥100 to <110 ml/ m^2 (male) or ≥90 to <100 ml/m^2 (female) • or RV ejection fraction >40% to ≤45%
Right ventricle ventriculography	
Regional RV akinesia, dyskinesia, or aneurysm	There are no minor criteria for ventriculography
II. Tissue characterization of wall	
• Residual monocytes <60% by morphometric analysis (or <50% if estimated) with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual monocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated) with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarisation abnormalities	
• Inverted T waves in right precordial leads (V1, V2 and V3) or • Beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120ms)	Inverted T waves in leads V1 and V2 in: • Individuals >14 years of age (in the absence of complete RBBB), or in V4, V5, or V6 • Inverted T waves in leads V1, V2 V3 and V4 in individuals >14 years of age in the presence of complete RBBB
IV. Depolarization /conduction abnormalities	
• Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG • Filtered QRS duration ≥114 ms • Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms • Terminal activation duration of QRS ≥55 ms
V. Arrhythmias	
• Nonsustained or sustained VT of LBB morphology with superior axis (negative or indeterminate QRS in leads II, III and aVF and positive in lead aVL)	• Non-sustained or sustained VT of RV Outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
• ARVC/D confirmed in a first degree relative who meets Any 1 of the following current Task Force criteria • Pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation categorized as associated with ARVC/D in the patient under evaluation	• History of ARVC/D 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/D confirmed pathologically or by current Task Force Criteria in second-degree relative

RV=Right ventricle; PLAX=Parasternal long-axis view; RVOT=Right ventricular outflow tract; BSA=Body surface area; PSAX=Parasternal short-axis view; RMS=Root means square.

ECG screening

In young people involved in competitive sports this simple method is still the main life-saving strategy. Namely, despite the non-specific nature of alterations, about 90% of patients will have a change in their ECG (8, 21). In Italy, where special attention is paid to the matter, it has been determined that just a correct ECG interpretation during screening decreases the yearly incidence of sudden deaths of athletes, because it detects potential patients before giving them a proper ARVC diagnosis (4). Still, initially about half the patients have a normal ECG. In others, ECG alterations may vary: a) negative T-waves in V1-V3 in persons older than 14; b) an epsilon-wave finding in V1-V3, 3) ventricular rhythm disturbances originating from the right ventricle. The QRS complex in V1-V3 is often dilated (≥110 ms). Sometimes a right bundle branch block is present. Negative T waves occur because of the altered histological structure of the myocardium. They are located in the right precordial leads, but also in limb leads. It seems that a negative T wave finding in more than 3 precordial leads has a significant predictive value for serious outcome prognosis (symptomatic arrhythmias, heart failure, fatal outcome), particularly if negative T-waves also exist in two or three inferior leads (likely connected with spreading to the left ventricle) (Fig. 2).

On the other hand, epsilon wave, T wave dispersion, or extra-systolic occurrence in the ECG, have no significant predictive value (22). An epsilon wave is a characteristic low amplitude signal located in the ST-segment, between the end of the QRS complex and the beginning of a T-wave. It may be found in 30% of patients. Epsilon waves are easier to notice if, while screening, one uses a high pass filter of 40 Hz, doubled amplitude signal display (20 mV/mm) and doubled recording speed (50 mm/s). It is also good to try to

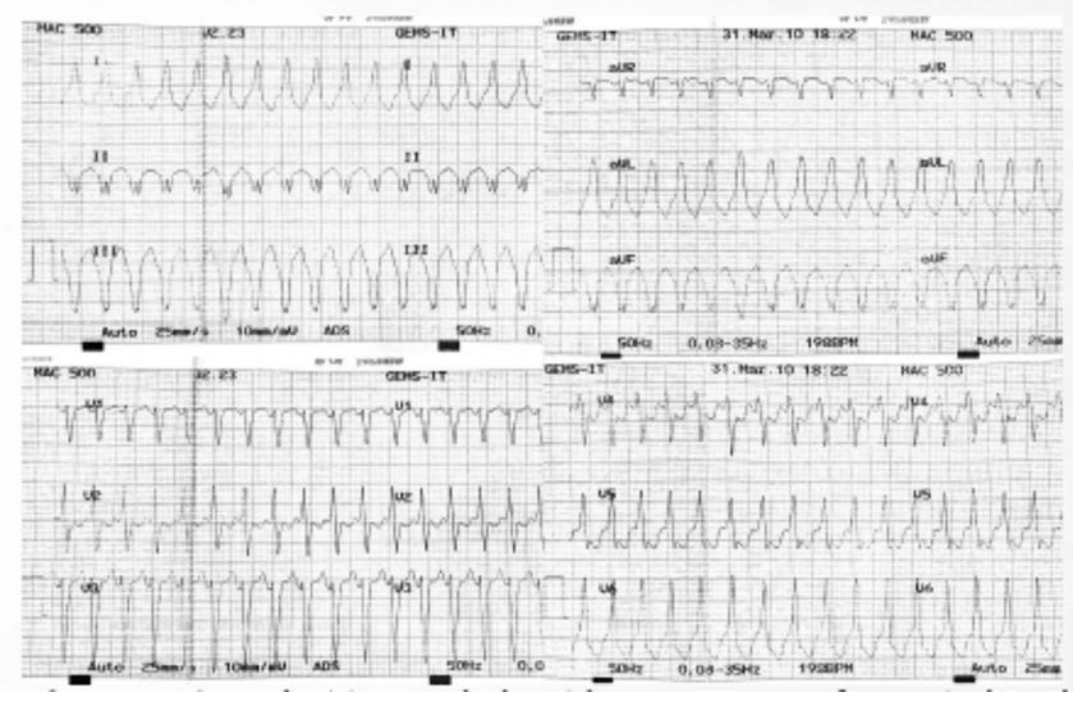

Fig. 2 *12-lead ECG recorded amid management of sport-induced cardiac arrest. The ECG shows broad complex tachycardia with LBBB morphology and superior axis, suggesting ventricular tachycardia originating from the right ventricle (from our own archives).*

screen the three "modified Lewis leads" (to move the right hand ECG electrode to the manubrium sternum, to place the left hand one onto the xiphoid ending, and put the left leg electrode onto the chest, between the usual positions for V4 and V5 screening. These custom recordings will show on the ECG at recording places I, II and III) (23). Epsilon waves are an expression of slow flow in the right ventricle, i.e. of the existence of an area of late depolarization in the right ventricle. For the same reason, an extended S-deflection (wave) may often be noticed. Ventricular tachycardia, except in rare cases, has a right ventricle vector (the appearance of a left bundle branch block, i.e. a positive deflexion in aVL). Tachycardia which does not have consistent QRS-complex morphology will arouse our suspicion, particularly if the QRS-vector of that tachycardia is directed upwards (negative QRS in II, III and avF). However, the vector may also be directed downwards, and then it appears as an ectopia seen along the idiopathic VT from the right ventricular outflow tract. Especially at the onset of the disease, ventricular ectopic activity may only be present in the right ventricular outflow tract, and so it may be difficult to distinguish between ARVC and benign idiopathic VT from the right ventricular outflow tract. One must be particularly careful not to confuse these two diseases. An ARVC sign on the ECG during tachycardia is a QRS-complex in the I lead longer than 120 ms, and sometimes a notch in the descending part of at least one QRS-complex may be seen. A transitional zone finding in V6 is rare, but also very specific (24). Much more clearly than ECG, imaging methods will sooner or later show at least some relatively typical structural changes: global or segmental right ventricle dilation with mandatory alterations to the the wall motion (hypokinesia, akinesia or aneurism); with or without a decrease in the outflow fraction; enveloping of the left ventricle.

Echocardiography

This is definitely the first image test we perform at the onset of the disease, but its sensitivity at that time is very low. By it we expect to discover structural changes – right ventricle dilation, the appearance of an aneurism (such changes are highly specific) – with the simultaneous existence of functional changes – decreased movement of the right ventricle wall, right ventricle failure, paradoxical septal motion or tricuspid regurgitation. Ways to evaluate echocardiography are listed exhaustively in the Working Group criteria (Table 1). Right ventricle dilation may also be found in other diseases (e.g. pulmonary hypertension) so it is imperative to determine additional functional changes (akinesia, dyskinesia, aneurism) for the finding to be ARVC specific. In later stages changes on the left ventricle may also be found.

Cardiac magnetic resonance (MR) and multidetector computed tomography (MDCT)

MR has several advantages when compared to echocardiography. First of all, it is possible to excellently display the heart and its relationship with other anatomical structures in 3D, so the quantification of the volumes of heart cavities does not rely solely on geometrical extrapolations. MR enables precise analysis of the ventricle volume, dilation, dysfunction, and the appearance of aneurisms can be precisely determined. With modern devices, with or without the use of gadolinium, it is possible to analyze the tissue of the wall of the heart, myocardium cell loss and infiltration of other cells (fibrosis and adipocytes). But the wall of the right ventricle is still very thin, so despite everything it remains difficult to distinguish between, for example, pericardial fatty tissue and fat infiltration, and the possibility remains of false interpretation (Fig. 3). Here the same rule as for echo so-

nography applies – it is necessary to display both the ventricle dilation and the changes in contractility. In patients where MR is contraindicated, the alternative method is MSCT. However, MR is the method of choice (25).

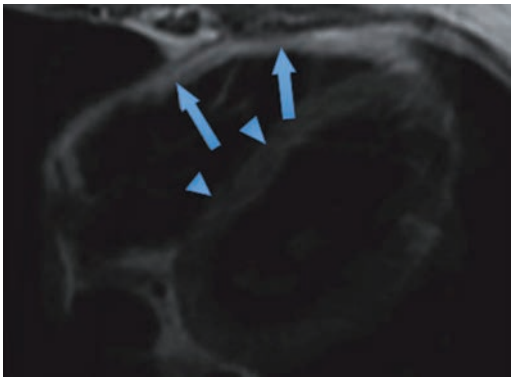

Fig. 3 *Black blood T1-weighted cardiac MR image showing diffuse fatty infiltration and thinning of right ventricle wall. Increased signal intensity in free wall (arrows) impaired with the intermediate signal intensity of the septum (arrowheads) is a sign of fatty infiltration (from our own archives).*

Electrophysiological heart examination

The indication for an electrophysiological study is essentially the appearance of VT. The typical mechanism of ARVC tachycardia is macro-reentry, and circling occurs around a block of connective or fatty tissue. In a myocardium altered by the disease such monomorphic tachycardia may "degenerate" into ventricular fibrillation, which is a likely mechanism of the sudden death of patients. Invasive electrophysiological heart examination, with an induced tachycardia, can help distinguish ARVC from idiopathic tachycardia of the right ventricular outflow tract, because the mechanism of the tachycardia is different. In that way, even if imaging methods have not resulted in a decisive finding, after the electrophysiological study and analysis of the mechanism of the induced VT, ARVC diagnosis becomes more certain. Also useful for these patients is a strategy of creating a voltage map RF-ablation of VT. A voltage map created during a study, if it uses electro-anatomic navigation (e.g. CARTO), will show zones of low amplitudes of electrical impulses. These "electrical grey zones" are in clear correlation with zones of structural changes detected by MR or biopsy, and will not be present in an idiopathic arrhythmia. The role of electrophysiological heart testing in anticipating malign arrhythmia occurrence is unclear. There are only a few studies, with opposing results and on a small sample of patients. It seems that ICD implantation in patients with inducible VT is justified due to symptomatic arrhythmia (26). However, we cannot either determine or refute an indication for inserting an ICD in a patient on the basis of the results of electrophysiological testing.

Screening late ventricular potentials

Late potentials are "minor" (low-voltage) electrical signals caused by fragmentation of electrical impulses during depolarization in the altered myocardium of the ventricle, and by precise screening they are determined within the last 40 ms of the duration of the QRS-complex. Due to this fragmentation, they indirectly indicate the existence of a substrate for impulse circling. Along with an additional trigger mechanism (e.g. extrasystole) there is a likelihood of a tachycardia. These potentials cannot be recognized by a regular survey by a standard ECG. Many modern ECG machines have software which supports this screening. Unlike the standard short ECG screening, this screening lasts for about 10 minutes because the device has to record approximately 250 QRS-complexes in order for it to compare and exclude artifacts caused by skeletal muscles as well as other disturbances. The device filters an accidental "murmur" and thus enables detection of an exceptionally low amplitude signal (not in

milli-, but in micro-volts) in the last part of the QRS-complex, which deviate from the standard values in healthy people. Although they are not pathognomonic, such potentials point to the possible existence of ARVC.

Right ventricle ventriculography

Biopsy is a method which provides high specificity for ARVC diagnosis, but unfortunately it lacks sensitivity, mostly because the path histological changes within the heart are not equally distributed. Besides, the usual locations for taking samples are not the locations where changes are expected in ARVC: the disease usually starts in the epicardium and only later spreads to the endocardium, and the interventricular septum is usually not encompassed until the final stages of the disease. Therefore, a biopsy is not a *conditio sine qua non* for a diagnosis. If ARVC is suspected, a sample for adequate analysis is taken from the lateral side of the right ventricle. During biopsy tissue analysis the pathologist will not only describe, but will also morphometrically quantify the proportion of remaining myocytes. Dead myocytes are replaced with connective tissue cells. Fatty cell findings are not necessary for a diagnosis (27).

Laboratory results

A useful marker for detecting right ventricle dysfunction is an elevated level of NT.pro-BNP. The level correlates with the degree of right ventricle dilation (28).

Genetic evaluation

Today genetic tests are routinely performed, and genetic changes can be determined with commercially available tests in up to 60% of ARVC patients. Genetic testing may be useful (class IIA) for ARVC confirmation in patients who have already met the criteria of the Working Group (21, 26). On the other hand, if a gene mutation is not confirmed, it does not exclude the existence of the disease. If probing within a family has determined a gene mutation, but the person has no symptoms, or does not meet the criteria, regular monitoring is required (bearing in mind the varied gene expression depending on age and clinical image diversity) (26).

Treatment

The most important step in approaching the patient is timely diagnosis. Then the treatment comes down to 1) prevention strategy with monitoring the course of the disease and 2) symptomatic treatment. Prevention strategy includes the following procedures:

- Lifestyle modification (primarily a ban on sporting competitions);
- Educating the patient (particularly recognizing alarming symptoms);
- Clinical monitoring (detection of arrhythmias, ECHO);
- Arrhythmia prophylaxis (beta blockers, ICD implantation, sotalol);
- Genetic counseling in family planning.

In some cases treatment for heart failure is required. Heart transplant is rarely required for treating heart failure or severe arrhythmias, but when it is, it is mostly in patients with early manifestations of the disease. Beta blockers or ACE-inhibitors are often used in these patients as well, in accordance with their application in decreasing the mortality of patients with heart failure, but no study has confirmed the decreased mortality in this group of patients (26). ICD implantation for secondary prevention is a necessity for each patient with identified VT or after ventricular fibrillation. If there is justified frequent ICD activation, arrhythmias may initially be regulated with solatol (classic ARVC medicine) or amiodarone (some reports indicate better results than with solatol). Indications for ICD

implantation in primary prevention are less clear. Justified ICD activations were observed in patients with inducible VT in an electrophysiological study, in those with inconsistent VT, syncope or frequent VES (26). If a person is an asymptomatic gene carrier, ICD implantation is not required (4). If medication-induced arrhythmia prophylaxis fails as the first line of treatment, and arrhythmias are frequent, a catheter RF-ablation may be used, using electro-anatomic navigation for easier locating of the arrhythmia "circle". But one must take into account that in this case catheter ablation is not curative but only a temporary measure until another arrhythmia "circle" appears. Physical exertions are to be avoided, with even recreational sports being prohibited. Patients who do not expose themselves to exertion have a five times lower death risk than those engaged in competitive sports (26)

NAXOS ISLAD DISEASE

It is an autosomal disease with arrhythmogenic cardiomyopathy of the right ventricle, but combined with skin and hair alterations. The disease was first described in 1986 in families of the inhabitants of a Greek island of Naxos, but today patients from other parts of the Mediterranean basin are also described (e.g. Israel, Turkey, Italy) (8). The possibilities of very diverse mutations of genes in charge of coding plakoglobin and desmoplakin have been found (9). Altered hair gives patients a typical appearance: it is partially light, curly, looks like wool or steel wire. Eyebrows are scarce, as is overall body hair. Diffuse keratoderma appears on the palms and soles where pressured. Skin alterations appear when a child starts walking, and heart disease manifests itself in early adolescence. ECG is altered in 90% of patients, and syncope and permanent VT appear (Fig. 4). The disease, as one would expect, first appears in the right ventricle. Beside fibrosis, in this case histological analysis has found frequent fatty infiltration. When untreated, death is usually caused by arrhythmia at young adult age (8, 9, 18).

CARVAJAL SYNDROM

If ARVC also has a palmoplantar keratoderma with distinctive hair features (woolly hair) it is described as the Naxos syndrome, but if cardiomyopathy spreads onto both ventricles, with even more severe changes on the left ventricle, the entity is referred to as the Carvajal syndrome. The disease was first described in 1998 in a group of patients from Ecuador, while in Europe it is most commonly described in the Mediterranean basin (Turkey, Greece, Italy) (8). Inheritance is au-

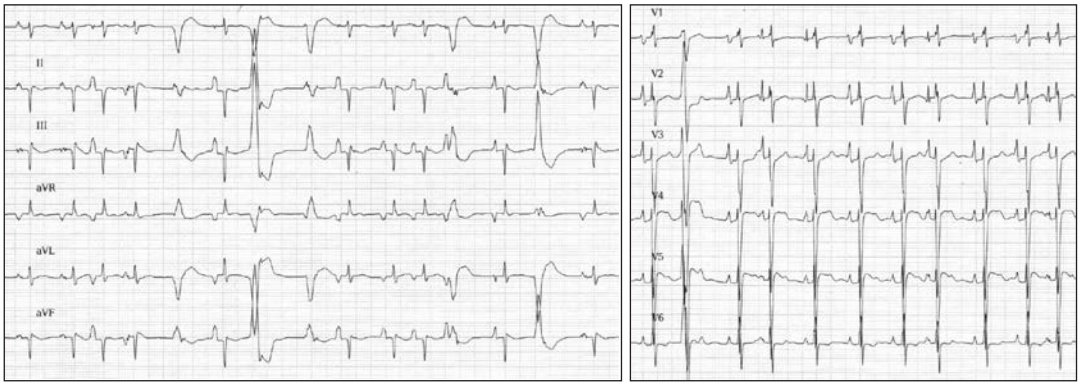

Fig. 4 *ECG showing sinus rhythm, right–axis deviation, tachycardia, low voltage in the leads in the extremities, T-wave inversion in leads V2 to V6, and a single ventricular extrasystole (from our own archives).*

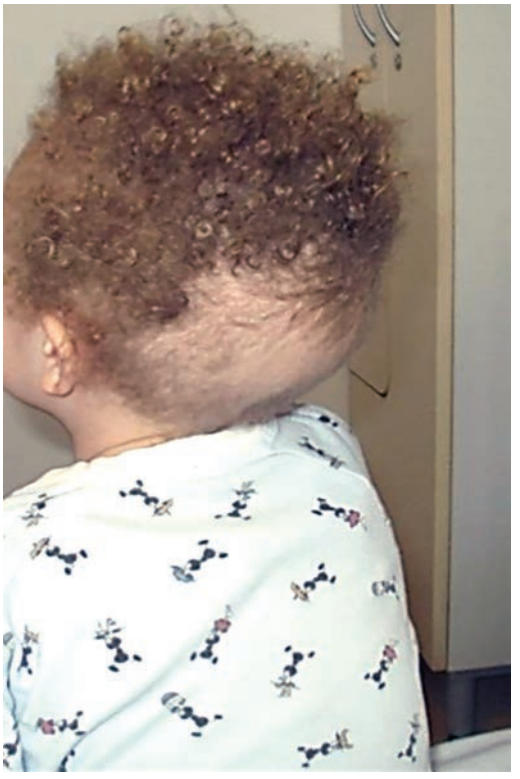

Fig. 5 *Posterior and view of the head of patient with Carvajal syndrome showing the characteristic woolly hair (from our own archives).*

tosomal recessive, and the mutation is in the desmoplakin gene (36). Genetic heterogeneity is less pronounced than in the Naxos syndrome. Patients are born with woolly or curly wire-like hair (Fig. 5).

After the first year (when the child starts walking) keratoderma, pronounced thickening of the skin on the soles and palms, appears. In most patients skin alterations are

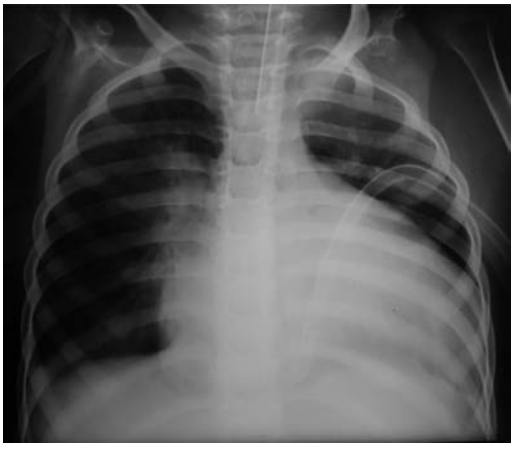

Fig. 6 *X-ray – Global enlargement of the heart and pulmonary edema (from own archives).*

visible before the appearance of cardiomyopathy which takes hold in both ventricles. The first to appear are asymptomatic arrhythmias. Typically, EKG shows "microvoltage" in the extremity leads, as well as negative T-waves in left precordial leads; x-ray shows global enlargement of the heart and pulmonary edema (LV insufficiency) (Fig. 6). Also early, approximately at the age of eight, the ejection fraction is significantly decreased because of progressive dilatation, primarily in the left ventricle (Fig. 7). Typically, the disease mostly attacks the left ventricle, with only fibrosis histologically present, while fat infiltration is rarely found (Fig. 8). In Carvajal syndrome, patients' signs of cardiomyopathy and heart failure appear earlier than in patients with Naxos syndrome. Untreated patients die earlier (33, 34, 35, 36).

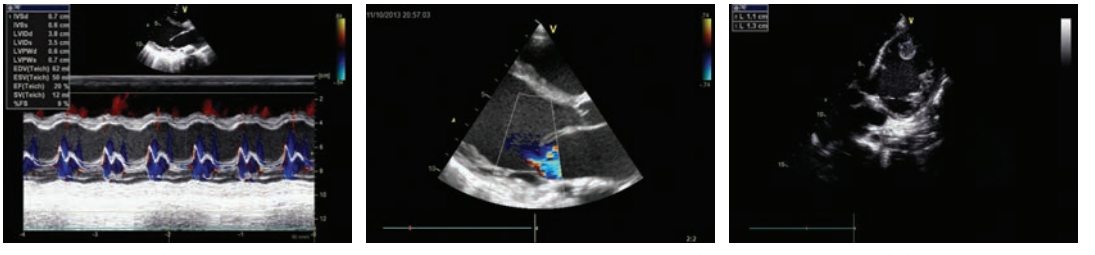

Fig. 7 *Echocardiographic images in the: 1. M- mode (EF 20%), paradoxical movement of the septum, 2. long axyis with global enlargement and mitral insufficiency and 3. 4-chamber orientation with global enlargement, low contractility and appearance of trombosis into the left ventricle (from own archives).*

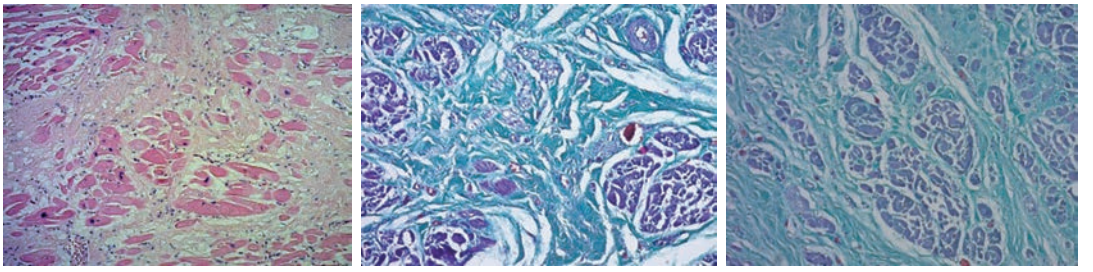

Fig. 8 *Histology: Haematoxilylin-eosin and Malory stained section LVPW, RV and IVS of pattient, showing extended fibrosis and replacement of the myocardium. Complete myocad containes a banndles of fibrous tissue, without fatty replacement. Augmentation 200× (from own archives).*

Conclusion

In patients with ARVC, symptoms and the age of disease onset vary significantly, but in most cases symptomatic and life-threatening arrhythmias appear sooner or later. If the disease is recognized on time and the patient is protected by ICD implantation, sudden death can be prevented. Early recognition and treatment change the natural progression of the disease significantly. Some entities, such as Carvajal syndrome, have worse prognosis than in most ARVC patients. The 2010 Working Group criteria enable diagnosing in childhood, thus improving the overall disease course and prognosis.

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References

1. Dalal D, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation. 2005;112(25):3823-32.
2. Saguner AM, Vecchiati A, Baldinger SH, Rüeger S, Medeiros-Domingo A, Mueller-Burri AS, et al. Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circ Cardiovasc Imaging. 2014;7(2):230-9.
3. Ruwald AC, Marcus F, Estes NA, Link M, McNitt S, Polonsky B, et al. Association of competitive and recre3rd ational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. Eur Heart J. 2015;36(27):1735-43.
4. Corrado D, Basso C, Thiene G. Arrhythmogenic right ventricular cardiomyopathy: an update. Heart. 2009;95(9):766-73.
5. Herren T, Gerber PA, Duru F. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a not so rare "disease of the desmosome" with multiple clinical presentations. Clin Res Cardiol. 2009;98(3):141-58.
6. Azaouagh A, Churzidse S, Konorza T, Erbel R. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update. Clin Res Cardiol. 2011;100(5):383-94.
7. Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol. 2007;50(19):1813-21.
8. Romero J, Mejia-Lopez E, Manrique C, Lucariello R. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D): A Systematic Literature Review. Clinical Medicine Insights: Cardiology. 2013;7:97-114.
9. Baykan A, Olgar Ş, Argun M, Özyurt A, Pamukçu Ö, Üzüm K, et al. Different clinical presentations of Naxos disease and Carvajal syndrome: Case series from a single tertiary center and review of the literature. Anatol J Cardiol. 2015;15(5):404-8.
10. Saffitz JE, Asimaki A, Huang H. Arrhythmogenic right ventricular cardiomyopathy: new insights

into mechanisms of disease. Cardiovasc Pathol. 2010;19(2):166-70.

11. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, et al. Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65(2):384-98.
12. Blomström-Lundqvist C, Sabel KG, Olsson SB. A long term follow up of 15 patients with arrhythmogenic right ventricular dysplasia. Br Heart J 1987;58(5):477-88.
13. Nava A, Thiene G, Canciani B, Martini B, Daliento L, Buja G, et al. Clinical profile of concealed form of arrhythmogenic right ventricular cardiomyopathy presenting with apparently idiopathic ventricular arrhythmias. Int J Cardiol. 1992;35(2):195-206.
14. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988 21;318(3):129-33.
15. Makanda A, Trémouroux-Wattiez M, Stijns-Cailteux M, de Jonghe D, Moretto M, Vliers A. Dysplasie arythmogène du ventricule droit chez un enfant de 16 mois. Arch Mal Cœur. 1989;82:811-14.
16. Pinamonti B, Sinagra G, Salvi A, Di Lenarda A, Morgera T, Silvestri F, et al. Left ventricular involvement in right ventricular dysplasia. Am Heart J. 1992;123(3):711-24.
17. Fontaine G, Fontaliran F, Frank R. Arrhythmogenic right ventricular cardiomyopathies: clinical forms and main differential diagnoses. Circulation. 1998;97(16):1532-5.
18. Protonotarios N, Tsatsopoulou A, Patsourakos P, Alexopoulos D, Gezerlis P, Simitsis S, Scampardonis G. Cardiac abnormalities in familial palmoplantar keratosis. Br Heart J. 1986;56(4):321-6.
19. Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. J Am Acad Dermatol, 1998;39(3):418-21.
20. Cabral RM, Wan H, Cole CL, Abrams DJ, Kelsell DP, South AP. Identification and characterization of DSPIa, a novel isoform of human desmoplakin. Cell Tissue Res- 2010;341(1):121-9.
21. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. Eur Heart J. 2010; 31:806-14
22. Saguner AM, Ganahl S, Baldinger SH, Kraus A, Medeiros-Domingo A, Nordbecka S, et al. Usefulness of Electrocardiographic Parameters for Risk Prediction in Arrhythmogenic Right Ventricular Dysplasia. Am J Cardiol. 2014;113:1728-34.
23. Fontaine G, Fontaliran F, Herbert JL, Cheamia D, Zenati O, Lecarpentier Y, et al. Arrthythmogenic right ventricular dysplasia. Annu Rev Med. 1999; 50:17-35.
24. Hoffmayer KS, Machado ON, Marcus GM, Yang Y, Johnson CJ, Ermakov S, et al. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract tachycardia. J Am Coll Cardiol. 2011;58(8):831-8.
25. Bluemke DA, Krupinski EA, Ovitt T, Gear K, Unger E, Axel L, et al. MR Imaging of arrhythmogenic right ventricular cardiomyopathy: morphologic findings and interobserver reliability. Cardiology. 2003;99(3):153-62.
26. James CA, Calkins H. Update on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C). Curr Treat Options Cardiovasc Med. 2013;15(4):476-87.
27. Asimaki A, Saffitz JE. The role of endomyocardial biopsy in ARVC: looking beyond histology in search of new diagnostic markers. J Cardiovasc Electrophysiol. 2011;22(1):111-7.
28. Cheng H, Lu M, Hou C, Chen X, Wang J, Yin G, et al. Relation between N-terminal pro-brain natriuretic peptide and cardiac remodeling and function assessed by cardiovascular magnetic resonance imaging in patients with arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 2015;115(3):341-7.
29. Pilmer CM, Kirsh JA, Hildebrandt D, Krahn AD, Gow RM. Sudden cardiac death in children and adolescents between 1 and 19 years of age. Heart Rhythm. 2014;11(2):239-45.
30. Tabib A, Loire R, Chalabreysse L, Meyronnet D, Miras A, Malicier D, et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. Circulation.2003;108(24):3000-5.
31. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scien-

tific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J. 1994;71(3):215-8.

32. Marcus FI, Edson S, Towbin JA. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol. 2013;61(19):1945-8.
33. Asimaki A, Syrris P, Wichter T, Matthias P, Saffitz JE, McKenna WJ. A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet. 2007;81(5):964-73.
34. Williams T, Machann W, Kühler L, Hamm H, Müller-Höcker J, Zimmer M, Ertl G, Ritter O, Beer M, Schönberger J. Novel desmoplakin mutation: juvenile biventricular cardiomyopathy with left ventricular non-compaction and acantholytic palmoplantar keratoderma. Clin Res Cardiol. 2011;100(12):1087-93.
35. Prompona M, Kozlik-Feldmann R, Mueller-Hoecker J, Reiser M, Huber A. Images in cardiovascular medicine. Magnetic resonance imaging characteristics in Carvajal syndrome (variant of Naxos disease). Circulation. 2007;116(20):e524-30.
36. Malčić I, Kniewald H, Jelić A, Fressart V, Jalašić D. Carvajal syndrome – rare entity of cardiocutaneous syndrome in a child from the Mediterranean part of Croatia – report on a new mutation of a desmoplakin gene. Cardiol Young. 2015;25 (Suppl 1), p86.