

Expert Perspective

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and Naxos Disease

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In 1982, Marcus and Fontaine reported 22 young adult patients, mostly men, with recurrent episodes of sustained ventricular tachycardia originating from the right ventricle.¹ The characteristic findings on the surface ECG in these patients were T-wave inversion in leads V₁-V₃ and the presence of post-excitation waves at the end of the QRS complex or at the beginning of the ST-segment. Because of the frequent recurrence of ventricular tachycardia that was unresponsive to medical treatment, the patients underwent ventricular incisions (ventriculotomy) based on epicardial mapping. The ventricular tachycardia usually originated from the outflow tract, apex or posterior wall of the right ventricle. Biopsies from these regions, obtained during surgery, revealed fibro-fatty replacement of myocardium. The authors named this condition "arrhythmogenic right ventricular dysplasia" (ARVD) as it was considered to be due to abnormal development of myocardium. However, the term "arrhythmogenic right ventricular cardiomyopathy" (ARVC) is nowadays considered more appropriate.²

In 1986, 9 patients with ARVC associated with a stereotype cutaneous phenotype (peculiar woolly hair and palmo-plantar keratoderma) were reported.³ The patients belonged to 4 families and were siblings or first cousins of each oth-

er, indicating an autosomal recessive type of inheritance. They presented the cutaneous phenotype from infancy and developed episodes of sustained ventricular tachycardia or sudden death during adolescence or young adulthood. The condition was named "Naxos disease", since the patients originated from the island of Naxos and were also first evaluated there.⁴ A histological and electrocardiographic study that compared Naxos disease with classical ARVC showed that the cardiomyopathy was identical in both.⁵⁻⁷ In 1995, the World Health Organisation classified ARVC among cardiomyopathies, with Naxos disease as its recessive form.⁸

Naxos disease was the first described inherited form of ARVC, which highlighted the latter's genetic substrate. Meanwhile it revealed a wide clinical spectrum of ARVC, including subclinical forms, arrhythmic forms with predominantly right ventricular involvement and a relatively good prognosis, and severe forms with diffuse biventricular involvement and heart failure requiring a differential diagnosis from dilated cardiomyopathy.^{3,9} The study of Naxos disease contributed greatly to our knowledge of ARVC, since the cutaneous phenotype enabled study of the cardiomyopathy from the subclinical stages.¹⁰ Finally, in 2000, Naxos disease revealed the first causative gene for ARVC, which encoded

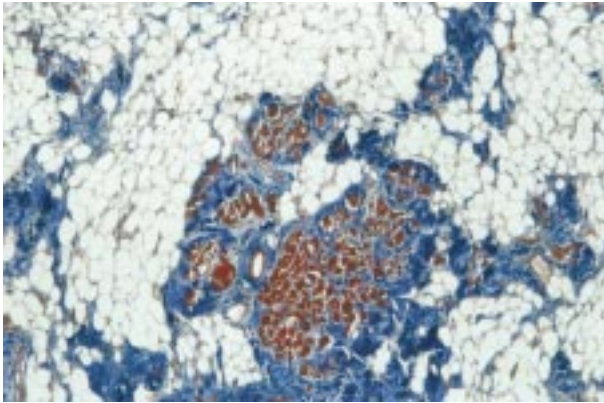


Figure 1. Typical histological findings of ARVC in a biopsy from the right ventricular wall of a patient with Naxos disease. There is extensive loss of myocardium that has been replaced by fatty tissue. Surviving myocardial fibres surrounded by fibrous tissue are embedded in fatty tissue producing a substrate of slow conduction and re-entrant ventricular arrhythmias (Heidenhain stain: fibrosis shown in blue and myocardial cells in red).

a cell-cell junction protein, and indicated that a cell adhesion defect might be a cause of cardiomyopathy.¹¹ Now, the model of the “broken heart” has opened up new roads to understanding the histopathology of myocardium and arrhythmogenesis.¹²

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC is an inherited structural disease of the heart muscle (*cardiomyopathy*) causing electrical instability resulting in life-threatening ventricular arrhythmias (*arrhythmogenic*) due to progressive structural and functional abnormalities of the right ventricle. Histological examination of the affected myocardium reveals loss of myocardial fibres and their replacement by fibro-fatty tissue. It initially affects localised areas of the right ventricle, particularly on the outflow tract, the posterior wall (below the tricuspid valve) and the apex (“triangle of dysplasia”).¹ Progressively, the disease extends globally throughout the right ventricle and may also affect the left ventricle, leading to severe biventricular involvement that needs to be differentiated from dilated cardiomyopathy.^{3,9} The affected wall shows dilatation, thinning and hypokinesia or dyskinesia resulting in compensating hypertrophy of the trabecular zone.¹ The interventricular septum is usually spared. The pathological process is characterised by progressive loss of myocardial fibres at subepicardial and mediomural layers with fibrous and fatty replacement² (Figure 1).

The relative contributions of these two types of repairing tissue may vary significantly.¹³

Regional differences in the prevalence of ARVC may result from a specific genetic substrate. In north-eastern Italy its prevalence reaches 1:5000. Studies of sudden death in young people showed ARVC to account for 20% of cases in north-eastern Italy² and for 42% in south-eastern Korea.¹⁴ Indeed, in north-eastern Italy it is the most common cause of sudden death in young athletes (22%),¹⁵ while in the USA it is a rare cause (3%).¹⁶ ARVC is reported to be inherited in more than 50% of cases with two types of transmission: autosomal dominant type with reduced penetrance (30-50%) and autosomal recessive type (Naxos disease).⁸

Naxos disease

Since 1995, according to the World Health Organisation’s classification, Naxos disease has been considered as the recessive form of ARVC.^{8,17} Naxos disease is a stereotype association of ARVC with a cutaneous phenotype, characterised by peculiar woolly hair and palmoplantar keratoses.³

Woolly hair appears from birth, whereas the keratoses develop during the first year of life when the infant starts to use hands and feet.¹⁸ The cardiomyopathy is clinically expressed after the twelfth year of life and shows 100% penetrance.¹⁹ The disease appears to have a more severe prognosis compared with the dominant form of AVRC.

Apart from Naxos, cases have also been reported from the Greek islands of Milos, Evia and Mykonos, as well as from south-eastern Turkey, Israel and Saudi Arabia.²⁰⁻²³ The prevalence of the disease in the Cyclades reaches 1:1000. A variety of Naxos disease (Carvajal syndrome) has been described in families from Ecuador and India. It clinically presents at a younger age, with more pronounced left ventricular involvement leading to heart failure, and exhibits a cardiac phenotype similar to that of dilated cardiomyopathy.²³

Molecular Genetics and Pathogenesis

Genetic studies have located two genes for the recessive form, encoding for the proteins plakoglobin and desmoplakin, and three genes for the dominant form, encoding for desmoplakin, plakophilin and ryanodine. Plakoglobin, plakophilin and desmoplakin are proteins of cell-cell adhesion, whereas

ryanodine is a protein of the sarcoplasmic reticulum that contributes to intracellular calcium transport.

A 2-base-pair deletion mutation of the plakoglobin gene (*Pk2157del2TG*) truncating the C-terminal of the protein causes recessive ARVC (Naxos disease).¹¹ This mutation was identified in 13 families from the Cyclades (Naxos, Milos, Mykonos) and in one family from Turkey (Kayseri).^{20,23} The prevalence of heterozygous carriers is up to 5% of the Naxos population. Heterozygotes present normal phenotype except for a small minority who show woolly hair as well as a few electrocardiographic or echocardiographic abnormalities not fulfilling the criteria for ARVC.¹⁹ Two different mutations of the desmoplakin gene (*Dsp7901del1G* and *DspG2375R*), truncating the C-terminal of the protein, have been found to underlie Naxos disease in families from Ecuador and Israel (Arab families),^{24,25} while a mutation (*DspS2994R*) that alters the N-terminal of the protein was found to be responsible for a dominant form of ARVC in families from the Veneto region in Italy.²⁶ Twenty-five heterozygous mutations of the gene encoding plakophilin-2 have been recently identified in 32 unrelated patients with ARVC from Germany (Gerull B, et al: *Nat Genet* 2004;36:1162-1164. Epub Oct 17, 2004). Mutation of the ryanodine-2 receptor gene has been implicated in an arrhythmogenic heart disorder that clinically resembles catecholaminergic polymorphic ventricular tachycardia rather than ARVC.²⁷

Myocardial cells are differentiated bipolar cells coupled at intercalated discs where adherence junctions, desmosomes and gap junctions are located.²⁸ Adherence junctions and desmosomes secure mechanical coupling while gap junctions serve electrical coupling. Plakoglobin (γ -catenin) is an intracellular protein of the adherence junctions and desmosomes. At the adherence junctions it is connected to the actin cytoskeleton and in the desmosomes to the intermediate filaments of desmin. Apart from its role in mechanical connection it has been also shown to have a signalling role to the nucleus. Thus the cells are informed about any change in their adhesion status and modify their behaviour accordingly, which can even lead to programmed cell death (apoptosis). Plakophilin is another desmosomal protein with properties similar to plakoglobin. Desmoplakin is also a cytoplasmic protein of the desmosomes that interlinks plakoglobin or plakophilin with desmin intermediate filaments. Defects in linking sites of these proteins can interrupt the contiguous chain of cell

adhesion, particularly under conditions of increased mechanical stress or stretch, leading to cell isolation and death, progressive loss of myocardium and fibro-fatty replacement.^{11,23} The degree of participation of fat in the repair process may be related to the rate of disease progression or may be mutation specific.²³ Surviving myocardial fibres within fibro-fatty tissue form zones of slow conduction and provide a substrate for re-entrant ventricular arrhythmias²⁹ (Figure 1). Recent studies on Naxos disease revealed that the genetically determined defect in cell adhesion results in gap junction remodelling and altered electrical coupling leading to a highly arrhythmogenic substrate.³⁰ The gap junctions are transmembrane channels consisting of the proteins connexins. Gap junctions serve the transfer of depolarising current between adjacent cells.³¹

Clinical expression and progression

ARVC is first clinically manifested during adolescence. Eighty percent of cases are diagnosed before the age of 40.³² An abnormal resting ECG has been reported in more than 90% of patients with the recessive form and in 50% of those with the dominant form of the disease.^{19,33}

The most frequent electrocardiographic findings consist of repolarisation abnormalities, with inverted T-waves, and of depolarisation abnormalities, with widening of the QRS complex (>110 ms) in leads V_1 to V_3 or more. The QRS complex in leads V_1 - V_3 is more than 25 ms wider than the QRS in lead V_6 (QRS dispersion). "Epsilon waves" are specific findings in these leads. They are low amplitude post-excitation waves appearing at the end of the QRS complex or at the beginning of the ST-segment (Figure 2). Epsilon waves are considered to be the result of delayed depolarisation (post-excitation) of the abnormal right ventricular myocardium.³⁴ The signal-averaged ECG reveals low amplitude (<40 mV) potentials at the final phase of the filtered QRS (late potentials), which correspond to the epsilon waves.³⁴ An electrocardiographic study in a genotyped population with Naxos ARVC showed that inverted T-waves in leads V_2 or V_3 , QRS prolongation (>110 ms) in leads V_1 - V_3 and ventricular extrasystoles with a left bundle branch block morphology showed the highest specificity and sensitivity, while epsilon waves, though absolutely specific, had a low sensitivity.³⁵ In a recent study, a prolonged S-wave upstroke (duration ≥ 55 ms) in leads V_1 - V_3 showed 98% specificity and 95% sensi-

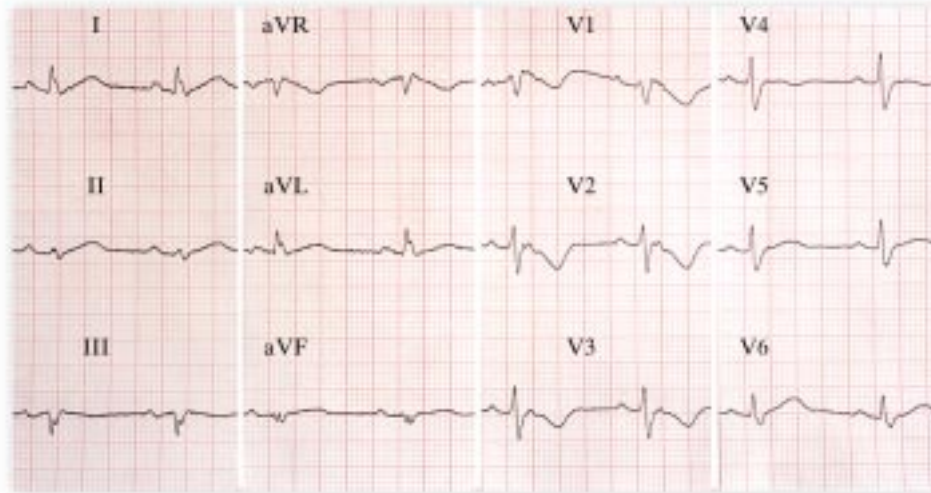


Figure 2. Resting 12-lead electrocardiogram (sensitivity 10 mm/mV, speed 25 mm/min) in a patient with ARVC (Naxos disease), showing inverted T-waves, widening of the QRS complex and post-excitation epsilon waves (end of QRS, beginning of ST) on the anterior precordial leads (V_1 - V_4). There is also low voltage, mainly on the limb leads, and left axis deviation (-30°).

tivity.³⁶ Other ECG findings are low voltage, the presence of a QS wave in leads V_1 - V_3 and inverted T-waves in the inferior leads.

All patients exhibit functional and morphological abnormalities of the right ventricular free wall, which can be detected by imaging techniques (two-dimensional echocardiography, magnetic resonance imaging, angiography). Regional or global hypokinesia, regional or global dilatation and aneurysms are among the characteristic findings of the disease¹⁹ (Figure 3). In the initial stages, the right ventricular abnormalities are localised to the “triangle of dysplasia” (outflow tract, posterior wall and apex) and may easily be misdiagnosed.

Symptoms appear during adolescence and are due to episodes of ventricular tachycardia. The most frequent symptom in teenagers is syncopal episodes. The majority of patients become symptomatic around the thirtieth year of life.^{19,33} The ECG during the symptomatic phase reveals sustained ventricular tachycardia with a left bundle branch block morphology and an inferior or superior axis. All symptomatic patients exhibit diagnostic findings on resting ECG and two-dimensional echocardiography.³⁴ Sudden death may be the first manifestation of the disease.³⁷

ARVC progresses with time and may result in severe involvement of the right or of both ventricles. More than 50% of patients with recessive ARVC

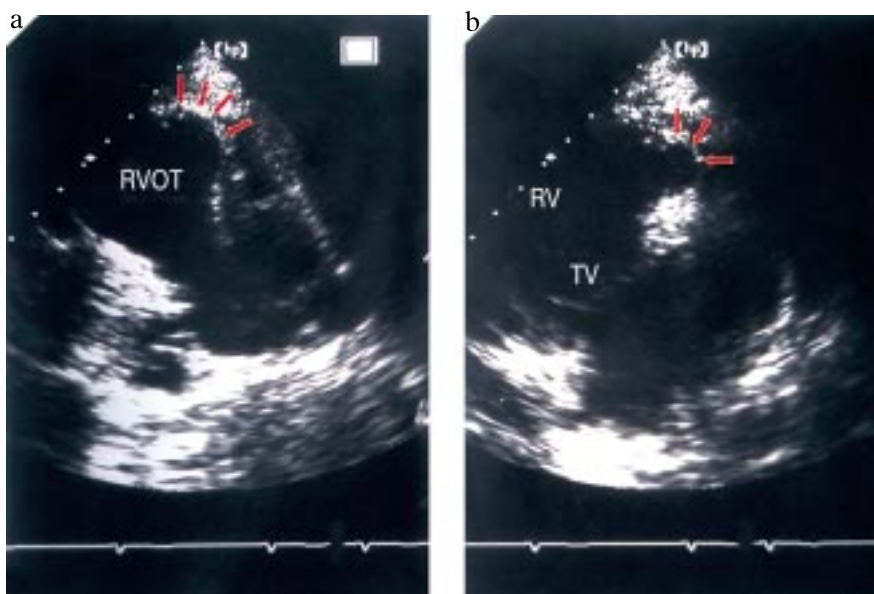


Figure 3. Two-dimensional echocardiography images from modified parasternal long axis view with the beam aiming upwards (a) or downwards (b). Aneurysms of the right ventricular free wall (arrow) can be seen on the outflow tract (a) and in-flow tract (b).

present heart disease progression during a mean follow-up period of 10 years.¹⁹ The progression appears to be stepwise, associated in some cases with an arrhythmic storm or sudden death.³⁴ Symptoms of heart failure, with fatigue, gastrointestinal disorders, hepatomegaly and ascites, appear in the final stages when the right or both ventricles are severely affected.³⁸ ARVC is one of the rare heart disorders causing heart failure without pulmonary hypertension.³²

Diagnosis

The candidate for ARVC diagnosis is usually a teenager or young adult suffering from unexplained syncope or episodes of sustained ventricular tachycardia of left bundle branch block morphology, an asymptomatic individual with frequent ventricular extrasystoles of the same morphology, or a member of a family with ARVC or juvenile sudden death. The arrhythmia and the family history steer us along the correct road to diagnosis. Relying mainly on morphological abnormalities of the right ventricle detected on echocardiography or magnetic resonance imaging (MRI) can be misleading.

In 1994 the Working Group on Myocardial and Pericardial Diseases of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology established criteria, major and minor, for the diagnosis of ARVC (Table 1).³⁹ The criteria are based on the presence and the characteristics of arrhythmia, on repolarisation abnormalities (resting ECG), on depolarisation abnormalities (resting and signal-averaged ECG), on structural/functional alterations of the right ventricle, on characteristic histological findings and on family history. Diagnosis requires the presence of 2 major criteria, or 1 major and 2 minor, or 4 minor criteria.

Diagnosis may be hampered by difficulties in validation of repolarisation abnormalities in the young, of minor right ventricular alterations and of findings in endomyocardial biopsy (false negative biopsy due to the regional involvement at subepicardial layers and the sparing of interventricular septum). The increasing application of MRI has shown that the method has extremely low specificity. In a recent study from Johns Hopkins University, 89 patients with an initial diagnosis of ARVC based on MRI findings were re-evaluated and the diagnosis was confirmed in only 27% of them.⁴⁰ None of 46 individuals diagnosed with ARVC based on the qualitative

finding of intramyocardial fat / wall thinning were ultimately diagnosed with ARVC. The authors emphasised that the findings of free wall thinning and/or increased intramyocardial fat signal on MRI are not part of the Task Force criteria, and that experts in the field do not recommend equating an intramyocardial fat signal on MRI to fat infiltration observed on biopsy. Therefore, the role of MRI should be limited to the detection of morpho-kinetic abnormalities of the right ventricular wall, contributing only to one of the criteria (minor or major) in the puzzle of ARVC diagnosis. However, in a recent study of 29 healthy individuals cardiac MRI detected right ventricular abnormalities in 93% of cases.⁴¹

Differential diagnosis of ARVC is needed in the minor form with mild right ventricular abnormalities, or in the severe form with diffuse biventricular involvement. In the former case the condition must be differentiated from arrhythmogenic situations with a structurally normal heart, such as right ventricular outflow tract tachycardia, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. In the severe form, the disease has to be differentiated from dilated cardiomyopathy. In arrhythmogenic conditions with a structurally normal heart the differential diagnosis is based mainly on electrocardiographic findings and the characteristics of the arrhythmia, while in dilated cardiomyopathy the diagnosis is based on the natural history of the disease and histopathology.

Arrhythmic Risk

ARVC is a mainly arrhythmogenic disorder causing fatal or nonfatal arrhythmic events. With an annual total cardiac mortality rate of 3%, the annual sudden death mortality reaches 2% or more.^{19,32} The mechanism of sudden death in ARVC is mostly acceleration of ventricular tachycardia with degeneration into ventricular fibrillation.³²

Studies from arrhythmia referral centres have shown that severe right ventricular dilatation appears to be a risk factor for arrhythmic events.⁴²⁻⁴⁴ However, a long-term study of an unselected population of patients with Naxos ARVC revealed that non-fatal arrhythmic events were related rather to a stepwise progression of the disease in the right ventricle than to severe but stable right ventricular dilatation.⁴⁵ It should be noted that at the end-stages of evolution, when the right ventricle is severely dilated and the patient is in heart failure, arrhythmic activity is al-

Table 1. Diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC).

1. Ventricular arrhythmias (with LBBB morphology)	
Frequent ventricular extrasystoles (ECG, Holter)	Minor
or	
Ventricular tachycardia (ECG, Holter, exercise test)	Minor
2. Repolarisation abnormalities	
Inverted T-wave in leads V ₁ , V ₂ and V ₃ in individuals aged over 12 years, without RBBB (ECG)	Minor
3. Depolarisation abnormalities	
QRS prolongation (>110 ms) in leads V ₁ -V ₃ (ECG)	Major
or	
Epsilon waves (ECG)	Major
or	
Late potentials (SAECG)	Minor
4. Morpho-kinetic abnormalities of the right ventricle (ECHO, MRI, ANGIO)	
Regional hypokinesia	Minor
or	
Mild segmental dilatation	Minor
or	
Mild global dilatation / hypokinesia	Minor
or	
Aneurysms (akinetic/dyskinetic areas with diastolic bulging)	Major
or	
Severe segmental dilatation (sacculation)	Major
or	
Severe global dilatation / hypokinesia	Major
5. Tissue characterization of walls	
Fibro-fatty replacement (endomyocardial biopsy)	Major
6. Family history	
Histologically diagnosed ARVC	Major
or	
Clinically diagnosed ARVC	Minor
or	
Premature sudden death due to suspected ARVC	Minor

ANGIO: angiocardiography, ECG: 12-lead resting electrocardiogram, ECHO: two-dimensional echocardiography, LBBB: left bundle branch block, MRI: magnetic resonance imaging, RBBB: right bundle branch block, SAECG: signal-averaged electrocardiogram.

most totally suppressed.^{38,46} In the same study of Naxos disease, QRS dispersion more than 40 ms on the resting ECG also appeared to be a risk factor for non-fatal arrhythmic events.⁴⁵

Risk factors for sudden death include severe arrhythmic events (syncopal episodes, ventricular tachycardia with haemodynamic compromise, cardiac arrest), the appearance of symptoms at a young age and the involvement of the left ventricle, as shown by both studies of Naxos disease¹⁹ and a recent report on sporadic cases of ARVC by Corrado et al.⁴⁷ The structural progression of the disease before the age of 35 years was another risk factor identified in patients with Naxos disease.¹⁹ Family history of sudden death and episodes of well-tolerated ventricular tachycardia did not appear to be related to sudden death. None of the asymptomatic patients

who received an implantable cardioverter defibrillator because of a family history of sudden death experienced appropriate interventions.⁴⁷ In the study by Corrado et al, ventricular tachycardia triggered in the electrophysiological laboratory did not appear to be a prognostic factor for ventricular fibrillation (and hence sudden death), since it showed a positive predictive value of 49% and a negative predictive value of 54%.⁴⁷ However, we believe that programmed electrical stimulation in asymptomatic patients may be of value for risk stratification and subsequent management. According to Wichter et al, inducible ventricular fibrillation during electrophysiological study was the only clinical variable that was associated with fast ventricular tachycardia/fibrillation recurrences during follow-up.⁴³ In conclusion, patients at high risk for sudden death are those: a) with episodes

of severe arrhythmic events (cardiac arrest, syncopal episodes, and spontaneous or induced ventricular tachycardia with haemodynamic compromise); b) who develop symptoms at an age less than 35 years; and c) with left ventricular involvement. At low risk are asymptomatic patients with structurally stable disease without left ventricular involvement, in whom programmed ventricular stimulation does not induce ventricular tachycardia with haemodynamic compromise.

Treatment

The fundamental objective in the treatment of patients with ARVC is the prevention of sudden death. The implantation of an automatic defibrillator seems to be the only treatment that effectively achieves this goal. The above-mentioned studies by Corrado⁴⁷ and Wichter⁴³ showed that implantation of a defibrillator increased the patients' 3-year survival by 24% and 32%, respectively. According to the available data, the indications for defibrillator implantation should be: 1) aborted sudden death; 2) syncopal episodes; 3) sustained ventricular tachycardia (spontaneous or induced) with haemodynamic compromise; 4) patient aged <35 years with symptoms or structural progression of the disease in the right ventricle; 5) patient with left ventricular involvement, irrespectively of symptoms or age.^{19,43,47,48} Here it must be stressed that a systematic study of the patient's family can prevent sudden death in affected members with non-diagnosed ARVC.

In patients with spontaneous or induced sustained ventricular tachycardia oral antiarrhythmic medication is given in order to prevent relapses. The drugs with the best results appear to be sotalol⁴⁹ and amiodarone, either alone or in combination with classical β -blockers.²⁹ The efficacy of the drug treatment should be guided by programmed ventricular stimulation. In case of frequent recurrences of sustained ventricular tachycardia in spite of the medication, radiofrequency ablation may be performed. The multiple morphologies of the tachycardia do not necessarily preclude ablation. Even if the initial ablation fails the subsequent drug treatment may be more effective.²⁹

In teenagers and young adults with ARVC reduction of myocardial wall stresses through the cessation of athletic activities and administration of β -blockers might delay the progression in cell adhesion defect. Carvedilol is being tested for this purpose be-

cause of its beta-blockade and reported anti-apoptotic properties. It would be interesting to study the effect of β -blockers in subclinical stages (teenage carriers of the abnormal genes) on disease progression. When heart failure has developed the classical treatment is applied, including medication and heart transplantation at the end-stages. If there is severe diffuse right or biventricular involvement anticoagulants are indicated to prevent pulmonary or arterial embolisms.

In an attempt to control Naxos disease, systematic screening of the populations at risk has been started in order to identify the heterozygous carriers of the plakoglobin gene mutation.

European Community Research Project for ARVC

Since 2000 a multicentre European study has been under way aiming to determine the clinical, pathological and genetic characteristics of ARVC, validate the diagnostic criteria and define strategies for disease treatment and prevention of sudden death.⁵⁰ Participants in this project are 7 referral centres from Italy, France, the United Kingdom, Greece (Yannis Protonotarios Medical Center, Naxos), Germany, Poland and Cyprus (<http://anpat.unipd.it/ARVC/>). Cardiologists who are treating patients with suspected or diagnosed ARVC are encouraged to make contact with their respective referral centres. All referral centres are currently updated with the new results of the study and any clinical recommendations regarding ARVC.⁵⁰

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