The right heart and pulmonary circulation (VIII)

Arrhythmia and Right Heart Disease: From Genetic Basis to Clinical Practice

Lucio Capulzini,* Pedro Brugada,* Josep Brugada,b and Ramón Brugadac

*aHeart Rhythm Management Centre, UZ- Brussels-VUB, Brussels, Belgium
*bServicio de Cardiología, Instituto Clínico del Tórax, Hospital Clínica de Barcelona, Barcelona, Spain
*cCentro de Genética Cardiovascular, Universidad de Girona, Girona, Spain

Historically, left ventricular cardiomyopathy and coronary heart disease have been regarded as the main causes of ventricular arrhythmia and sudden cardiac death. However, within the last two decades, arrhythmias originating from the right ventricle have begun to attract the attention of the scientific world for a number of reasons. Ventricular arrhythmias originating from the right ventricle usually affect younger patients and can lead to sudden cardiac death. The pathophysiologic mechanism of these arrhythmias is not fully understood, which can leave room for a range of different interpretations. Moreover, the intriguing world of genetics is increasingly being drawn into the pathogenesis, diagnosis and prognosis of some of these arrhythmias. This review considers the pathogenesis, diagnosis and treatment of arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVD), Brugada syndrome, right ventricular outflow tract ventricular tachycardia, and arrhythmias in the right side of the heart due to congenital heart disease. In addition, because ventricular arrhythmias associated with right ventricular heart diseases such as Brugada syndrome and ARVD can explain up to 10-30% of sudden cardiac deaths in young adults in the general population and an even greater percentage in young athletes, this article contains a brief analysis of screening tests used before participation in sports, life-style modification, and treatment options for athletes affected by these conduction disorders.

Key words: Arrhythmogenic right ventricular dysplasia. Brugada syndrome. Idiopathic right ventricular tachycardia. Sudden cardiac death.

INTRODUCTION

Left ventricular cardiomyopathy and ischemic heart disease have typically been considered the primary causes of ventricular arrhythmias (VAs) and sudden cardiac death (SCD). However, arrhythmias originating in the right ventricle (RV) have attracted the attention of scientists...
ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD) is characterized by VAs and progressive structural abnormalities of the RV.\(^1,2\) Myocardial degeneration may extend to the left ventricle, especially in advanced stages of the disease.\(^3\) ARVD can exist in both sporadic and familial forms. The disease is characterized by either massive or partial progressive replacement of myocardium by fatty or fibro-fatty tissue. This infiltration provides a substrate for electrical instability and leads to VAs ranging from isolated premature ventricular contractions (PVC) to sustained VTs or ventricular fibrillation.\(^3,4\) The prevalence of the disease in the general population has been estimated to range from 1 in 2000 to 1 in 10,000. Eighty percent of cases are diagnosed in patients under 40 years of age. ARVD should be suspected in all young patients with an apparently normal heart presenting with syncope, VT, or cardiac arrest. As will be discussed, the disease should also be suspected in athletes presenting with symptoms indicative of arrhythmias (palpitations, syncope).

Genetic Aspects

ARVD is a heritable condition.\(^5\) There is a high familial incidence (30%-50% of cases) with autosomal-dominant inheritance, various degrees of penetrance, and polymorphic phenotypic expression. An autosomal-recessive form of ARVD has also been described which is associated with palmoplantar keratoderma and woolly hair (Naxos disease).\(^6\) This type of ARVD is caused by a mutation in the plakoglobin gene, the product of which is a component of desmosomes and adherens junctions.\(^7\) The first mutation causing nonsyndromal ARVD was reported by Rampazzo et al in 2002.\(^8\) The mutation was found in the desmoplakin gene, encoding a component of the desmosome. In 2004, Gerull et al described 25 mutations in the cardiac desmosomal gene plakophilin 2.\(^9\) Desmocollin 2 and desmoglein 2, other putative disease-causing mutations in plakoglobin and desmoplakin, as well as in other desmosomal genes, were later identified in patients with nonsyndromal ARVD.\(^10\) Nowadays, desmosomal dysfunction is considered the final common pathway of ARVD pathogenesis.

Different genetic variants of ARVD have been mapped and over 140 disease-causing ARVD mutations have been published, the vast majority encoding desmosomal proteins. Some nondesmosomal genes have also been associated with autosomal dominant ARVD, such as the transforming growth factor β-3 gene (TGF β3),\(^11\) which modulates the expression of cell-contact proteins and the ryanodine receptor 2 (RyR2) gene.\(^12\) First described in 8 families, the RyR2 encodes receptors involved in calcium release from the sarcoplasmic reticulum. However, opinions still differ as to whether patients with RyR2 mutations should be considered as suffering from ARVD or from a catecholaminergic polymorphic VT. The most recently described mutation in the TMEM43 gene is responsible for a highly lethal and fully penetrant ARVD variant (ARVD5).\(^13\)

Desmosomes and ARVD

The structural and functional integrity of cardiac tissue is supported by desmosomes, adherens junctions and gap junctions located at intercalated disks (Figure 1). Desmosome integrity is required to maintain the normal function of gap junctions as intercellular channels responsible for the electrical coupling and signaling mechanisms in the regulation of cell growth, differentiation and development.

Genetic mutations responsible for ARVD result in haploinsufficiency and reduced expression of desmosomal proteins, which may
RV inflow tract adjacent to the tricuspid valve, but it also affects the anterior infundibulum and the apex, thus forming what is known as the “triangle of dysplasia.” Loss of myocardium may result in focal thinning of the ventricular free wall, focal bulging of the RV wall in diastole, and right ventricular outflow tract (RVOT) enlargement. Functionally, the disease may result in global or regional contraction abnormalities, RV systolic/diastolic function, RV aneurysm formation, and RV dilatation and hypokinesis. The interventricular septum is generally spared. Endomyocardial biopses, which are usually obtained from the septum, may therefore be non-diagnostic. Endomyocardial biopsy performed in the RV has low sensitivity because of the segmental nature of the predispose mechanical cell contacts to rupture, potentially triggered by mechanical stress of the RV (such as that occurring during exercise or sports activity). Degeneration and death of the cardiomyocytes is the pathological consequence of these mutations in adhesion proteins, with the subsequent progressive replacement by fatty and fibro-fatty tissue.

**Structural Abnormalities**

ARVD is characterized by replacement of myocardium with fatty and fibrous tissue that initially affects the epicardium and then the endocardium. This process most commonly involves the posterior and inferior areas of the RV inflow tract adjacent to the tricuspid valve, but it also affects the anterior infundibulum and the apex, thus forming what is known as the “triangle of dysplasia.” Loss of myocardium may result in focal thinning of the ventricular free wall, focal bulging of the RV wall in diastole, and right ventricular outflow tract (RVOT) enlargement. Functionally, the disease may result in global or regional contraction abnormalities, RV systolic/diastolic function, RV aneurysm formation, and RV dilatation and hypokinesis. The interventricular septum is generally spared. Endomyocardial biopses, which are usually obtained from the septum, may therefore be non-diagnostic. Endomyocardial biopsy performed in the RV has low sensitivity because of the segmental nature of the...
fatigue, atypical chest pain, syncope, and SCD. Age at the time of the first manifestation ranges between 15 and 35 years. Men are more frequently affected than women and usually present with more extensive disease. Symptomatic heart failure is an unusual manifestation of ARVD and usually occurs in more advanced stages of the disease. Patients with a long history of ARVD frequently show involvement of the left ventricle with clinical symptoms of biventricular heart failure.16

**Clinical Presentation**

ARVD usually presents with VTs with left bundle branch block (LBBB) morphology, originating from the RV, in apparently healthy adolescents or young adults. The VAs may be asymptomatic and detected by routine electrocardiogram, or they may cause palpitations, syncope or SCD. It has been estimated that ARVD accounts for up 5%-20% of SCD in individuals under 35 years of age.15 However, the clinical manifestations of the disease may vary widely in time of onset and degree of severity. The interaction between different genetic substrates with various degrees of penetrance and the presence of external triggers (such as strenuous exercise or vigorous training) explains the broad spectrum of clinical presentations, which can include palpitations, fatty infiltration. Samples should be retrieved from the RV free wall, as the fibro-fatty replacement is usually transmural and thus detectable from the endocardial approach. The risk of perforation during RV endocardial biopsy in the apex and free wall of the RV should not be underestimated.

**Diagnosis**

According to McKenna et al’s 1994 ARVD Task Force Report, diagnosis of ARVD should be based on the presence of structural, histological, electrocardiographic, arrhythmic, and genetic factors as well as on family history (Table 1). Patients must have either 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria to be considered as affected by ARVD.17 A modification of the Task Force Criteria for the diagnosis of ARVD was proposed in 2002 to take into account the case of first degree family members of a proband. In the latter case, the presence of right precordial T wave inversion (V2-V3), late potentials on signal-averaged ECG, or VT with LBBB morphology, or mild functional or morphological changes of the RV on imaging,

### TABLE 1. Task Force Criteria for Diagnosis of Arrhythmogenic Right Ventricular Dysplasia. (McKenna et al17)

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>Epsilon waves or localized prolongation (&lt;110 ms) of QRS complex in right precordial leads (V1-V3)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Sustained or nonsustained LBBB-like ventricular tachycardia documented on ECG or Holter monitoring or during exercise testing. Frequent ventricular extrasystoles (1000/24 h) on Holter</td>
</tr>
<tr>
<td>Global or Regional dysfunction and structural abnormalities</td>
<td>Severe dilatation and reduction of RV ejection fraction with no or mild LV involvement. Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulgings). Severe segmental dilatation of RV.</td>
</tr>
<tr>
<td>Tissue characteristics of walls</td>
<td>Fibro-fatty replacement of myocardium on endomyocardial biopsy</td>
</tr>
</tbody>
</table>

ARVD indicates arrhythmogenic right ventricular dysplasia; LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle.
ECG abnormalities may be present according to disease extension. However, the presence of a normal ECG should not preclude diagnosis of a preliminary form of ARVD.

**Imaging Evaluation**

Imaging techniques for diagnosing morphofunctional abnormalities consistent with ARVD include conventional angiography, echocardiography, computed tomography, radionuclide angiography, and magnetic resonance imaging (MRI). Right ventricular angiography has historically been regarded as the best imaging test for the diagnosis of ARVD and has been shown to be highly specific (90%).

Echocardiography is less invasive and represents the first-line approach in evaluating patients with suspected ARVD or in screening family members. MRI has the ability to differentiate fat from muscle and allows for a highly accurate and quantitative evaluation of RV size and function. Although the utility of MRI in ARVD diagnosis is well recognized, this technique sometimes leads to over-diagnosis of ARVD. The sensitivity and specificity of MRI for detecting RV intramyocardial fat in the diagnosis of ARVD is variable, ranging from 22% to 100%. Identifying fat can be challenging because the RV is a thin structure and areas of affected myocardium can be quite small. Moreover, it is now well known that it may be normal for fat to be present in the RV myocardium. Distinguishing pathologic adipose infiltration in areas where adjacent epicardial fat is normally present, such as in the AV groove and the antero-apical portion of RV, may be particularly difficult. Isolated areas of fat replacement have also been reported in elderly patients, in those with long-term steroid use, in obese individuals, in those with

**Electrocardiographic Abnormalities**

The electrocardiogram in patients with ARVD usually shows a regular sinus rhythm, with a QRS duration over 110 ms in lead V1. Electrocardiographic changes include inverted T waves in the right precordial lead beyond V1 in the absence of right bundle branch block (RBBB) and right ventricular late potentials in the form of “epsilon waves” in leads V1-V3 (Figure 2).

T wave inversion in leads V1-V3 is a well recognized ECG feature of ARVD and in the absence of RBBB is currently proposed as a major diagnostic criterion. The juvenile pattern of T wave inversion in V1-V3 or beyond is a normal variant in children under 12 years of age. This variant is present in 1%-3% of the healthy population aged 19 to 45 years and 87% of patients with ARVD. Epsilon waves are “postexcitation” electrical potentials of small amplitude that occur in the ST segment after the end of the QRS complex. Epsilon waves, which are seen in 33% of patients with ARVD, are considered a major diagnostic criterion for ARVD. Different ECG abnormalities may be present according to disease extension. However, the presence of a normal ECG should not preclude diagnosis of a preliminary form of ARVD.

![Figure 2. The ECG is from a 21-year-old male with arrhythmogenic right ventricular dysplasia. Right bundle branch block, epsilon wave (arrow) and diffuse T wave inversion are present.](image-url)

<table>
<thead>
<tr>
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<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>ARVD confirmed in a first degree relative who meets current Task Force Criteria</td>
<td>History of ARVD in a first degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria</td>
</tr>
<tr>
<td>ARVD confirmed pathologically at autopsy or surgery in a first-degree relative</td>
<td>Premature sudden death (&lt;35 years of age) due to suspected ARVD in a first degree relative</td>
</tr>
<tr>
<td>Identification of a pathogenetic mutation categorized as associated or probably associated with ARVD in the patient under evaluation</td>
<td>ARVD confirmed pathologically or by current Task Force Criteria in second-degree relative</td>
</tr>
<tr>
<td><strong>ECG abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of T wave) in the right precordial leads (V1-V3)</td>
<td>Late potentials by SAECG in ≥ 1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG.</td>
</tr>
<tr>
<td>Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)</td>
<td>Filtered QRS duration ≥114 ms</td>
</tr>
<tr>
<td><strong>Arrhythmias</strong></td>
<td></td>
</tr>
<tr>
<td>Nonsustained or sustained ventricular tachycardia of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, aVF and positive in aVL)</td>
<td>Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, aVF and negative in aVL) or of unknown axis</td>
</tr>
<tr>
<td>Residual myocytes &lt;80% by morphometric analysis (or &lt;50% if estimated), with fibrous replacement of the RV free wall myocardium in &gt;1 sample, with or without fatty replacement of tissue on endomyocardial biopsy</td>
<td>Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in &gt;1 sample, with or without fatty replacement of tissue on endocardial biopsy</td>
</tr>
<tr>
<td><strong>Tissue characteristics of walls</strong></td>
<td></td>
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<td>Fibro-fatty replacement of myocardium on endomyocardial biopsy</td>
<td></td>
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<tr>
<td><strong>Global or regional dysfunction and structural abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>By 2D echo</td>
<td></td>
</tr>
<tr>
<td>Regional RV akinesia, dyskinesia, or aneurism and 1 of the following (end diastole):</td>
<td>Regional RV akinesia, dyskinesia and 1 of the following (end diastole):</td>
</tr>
<tr>
<td>PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m²)</td>
<td>PLAX RVOT ≥29 to &lt;32 mm (corrected for body size [PLAX/BSA] ≥16 to &lt;19 mm/m²)</td>
</tr>
<tr>
<td>PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m²)</td>
<td>PSAX RVOT ≥32 to &lt;36 mm (corrected for body size [PSAX/BSA] ≥18 to &lt;21 mm/m²)</td>
</tr>
<tr>
<td>Fractional area change ≥33%</td>
<td>Fractional area change &gt;33% to ≤40%</td>
</tr>
<tr>
<td>By MRI</td>
<td></td>
</tr>
<tr>
<td>Regional RV akinesia or dyskinesia or dysynchronous RV contraction and 1 of the following:</td>
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</tr>
<tr>
<td>Ratio of RV end-diastolic volume to BSA ≥110 mL/m² (male) or ≥100 mL/m² (female)</td>
<td>Ratio of RV end-diastolic volume to BSA ≥100 to &lt;110 mL/m² (male) or ≥90 to &lt;100 mL/m² (female)</td>
</tr>
<tr>
<td>RV ejection fraction ≤40%</td>
<td>RV ejection fraction &gt;40% to ≤45%</td>
</tr>
<tr>
<td>By RV angiography</td>
<td></td>
</tr>
<tr>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
</tr>
</tbody>
</table>

ARVD indicates arrhythmogenic right ventricular dysplasia; BSA, body surface area; LBBB, left bundle branch block; PSAX, parasternal short-axis view; PLAX, parasternal long-axis view; RV, right ventricle; RVOT, RV outflow tract; SAECG, signal-averaged electrocardiogram.

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of low voltage RV regions, ie, electroanatomical scarring (Figure 3). In ARVD patients, RV scarring identified with electroanatomical mapping has been shown to correspond to areas of myocardial depletion and to correlate with the histopathologic finding of myocardial atrophy and fibro-fatty replacement at endomyocardial biopsy.

Corrado et al demonstrated that voltage mapping can be useful in the differential diagnosis between RVOT-VT and the early form of ARVD. In fact, in patients with VAs from the RV and an apparently normal RV using conventional imaging, the presence of an area of low voltage regions in the RVOT identified a subgroup at high risk for VT recurrence and SCD during clinical follow-up.

Very recently, Wijnmaalen et al showed that patients with scar-related right ventricular tachycardia with or without an established ARVD diagnosis according to the Task Force criteria had a higher VT recurrence rate than patients without electroanatomical scarring in the RV. These data confirm that voltage mapping might be an important diagnostic tool with prognostic and therapeutic implications.

**Voltage Mapping: an Important Diagnostic Tool**

Emerging data suggest an increasing role for endocardial voltage mapping in identifying the presence of scarring in the RV in early phases of the disease. The technique has the potential to accurately identify the presence, location and extent of the pathologic substrate of ARVD by demonstration of other cardiomyopathies, and in idiopathic RVOT-VT. Physicians should therefore avoid a diagnosis of ARVD when the only structural abnormalities are those seen on MRI.

Late-gadolinium-enhanced MRI can localize fibro-fatty changes in the RV myocardium. The fibro-fatty variety of ARVD is more common than fatty ARVD. Thus, a potential role of late-gadolinium-enhanced MRI may be to detect early and subtle cases of ARVD which may otherwise be misdiagnosed.

Documentation of fibrous tissue has been suggested to be diagnostically more important than finding fat alone.

![Figure 3. Above: voltage mapping reconstruction of the right ventricle in sinus rhythm using an electroanatomical mapping system (Carto 3, Biosense Webster, USA) in a 43-year-old man with an overt form of arrhythmogenic right ventricular dysplasia and a symptomatic monomorphic ventricular tachycardia. Areas of scar are identified (local voltage <1.5 mv) at the right ventricle antero-lateral wall (basal part). Red dots represent the radiofrequency ablation line delivered with the intent to block the scar-related macro reentry circuit. Below: endocavitary late potentials recorded from the mapping catheter in and around the scar regions.](image)
Differential Diagnosis

The main differential diagnoses of ARVD are RVOT-VT, sarcoidosis, idiopathic dilated cardiomyopathy, and isolated myocarditis. Both RVOT-VT and ARVD occur in young, apparently healthy individuals, and both may present with PVCs or VT with a LBBB and inferior axis. Although it is not difficult to diagnose a manifest case of ARVD, differentiation of ARVD at its early stages from RVOT tachycardia, a usually benign and nonfamilial arrhythmic condition, remains a clinical challenge. If clinical doubts remain after traditional examinations (ECG, Holter) and imaging techniques (echocardiogram, right ventricular angiography, MRI), RV voltage mapping seems to be a useful emerging tool to differentiate between the 2 entities.

Role of Genetic Analysis

A key clinical application of genetic analysis includes confirmatory testing of proband cases to facilitate interpretation of borderline investigations and cascade screening of relatives. Genotyping relatives before a malignant clinical phenotype is manifest may be crucial in preventing SCD. Management of relatives with non-overt forms of ARVD diagnosed by molecular genetic analysis may prevent SCD in these subjects through serial clinical follow-up (electrocardiogram, echocardiogram, 24-hour Holter, early recognition of symptoms), lifestyle modifications (restriction from extreme activity), and prophylactic therapy when needed (antiarrhythmic drugs, implantable cardioverter-defibrillators [ICD]). Despite its reliability, genetic sequencing is an effort- and cost-intensive process, especially in the investigation of ARVD, in which potentially large numbers of genes are involved.

Very recently, a new diagnostic test based on immunohistochemical desmosomal analysis of human myocardial samples obtained by endomyocardial biopsy has been reported in a small patient population. This study showed that the immunoreactive signal level for the desmosomal protein plakoglobin was reduced at intercalated disks in patients with ARVD. Interestingly, plakoglobin signal levels were reduced not only in right ventricular myocardium showing typical pathological changes of fibro-fatty replacement but also in normal-appearing left ventricle and interventricular septum. Moreover, this was not observed in others forms of heart-muscle disease.

Risk Stratification

The available data suggest that severe RV dysfunction, left ventricle involvement, syncope, young age, male sex, prior cardiac arrest, fast and poorly tolerated VT with different morphologies, and familial occurrence of juvenile sudden death are the major factors in determining a poor outcome. High-risk patients present with clinical signs of right heart failure and/or have left ventricular dysfunction and a history of VT. These patients should be regarded as candidates for aggressive therapeutic management. Conversely, patients without VT are at very low risk of cardiac events. Debate is still on-going as to whether electrophysiological study is useful or in predicting the occurrence of VT during follow-up. Lifestyle recommendations, i.e. restrictions on vigorous physical activity, may improve the long-term outcome.

Treatment

The main goal of a management strategy is to prevent SCD. Currently, antiarrhythmic drugs, catheter ablation, and ICDs are the 3 main therapies available for patients with ARVD.

Antiarrhythmic Drugs

Patients with ARVD and no history of syncope or cardiac arrest, but with PVCs, couplets or short ventricular runs do not usually have an increased risk of arrhythmias and therefore do not require specific antiarrhythmic treatment. In patients with sustained VT, the aim of antiarrhythmic drug therapy is not so much the suppression of VT recurrences but the prevention of SCD. Sotalol at a dosage of 320-480 mg/day was identified as the most effective drug, resulting in a 68% overall efficacy rate. Interestingly, a recent study in a cohort of rigorously characterized ARVD patients showed that beta blockers were neither harmful nor protective against clinically relevant VAs, that sotalol was not effective, and that amiodarone had the greatest efficacy. Class I antiarrhythmic drugs proved effective in only a minority of patients with ARVD. To date, prospective, randomized studies on antiarrhythmic drug efficacy in ARVD are not available.

Catheter Ablation

Current indications for catheter ablation in patients with ARVD include monomorphic and well tolerated VT with localized forms of the disease and drug-refractory or incessant VT or frequent ICD discharges. In the latter, catheter ablation can play an important role as a palliative or an adjunctive treatment option for reduction or suppression of the VT. VT in ARVD is the result of a scar-related macro-reentry circuit, similar to that observed in
not yet been defined. In the future, it is likely that genetics will play a more important role in decision-making.\textsuperscript{46,47} Of note, ICD implantation in patients with ARVD may lead to complications more frequently than in other diseases requiring an ICD. A common complication is related to the progression of myocardial atrophy and subsequent replacement by fat at the site of lead implantation. This results in a loss of the sensing function in the right ventricular defibrillation lead, with a concomitant need for lead revision. Therefore, when deciding on whether to use ICD therapy in ARVD, the potential benefits should be weighed against the risk of complications.

When the disease has progressed to right ventricular or biventricular failure, treatment consists of the current therapy for heart failure, including diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and anticoagulants. In the case of intractable right heart failure, cardiac transplantation may be the only alternative.

**BRUGADA SYNDROME**

**Introduction**

Brugada syndrome (BS) is a genetic disease which causes cardiac arrhythmias and is characterized by the occurrence of SCD in young individuals.
without evidence of structural heart disease. Due to the macroscopic absence of structural heart abnormalities, BS is classified as a “primary electrical disease” or cardiac channelopathy. BS is related to structural and functional abnormalities in the sodium channel. Different pathophysiological findings suggest that the electrical disorders associated with BS are mainly located in the RV and particularly in the RVOT.

Patients with BS present an ECG pattern characterized by ST segment elevation in the right precordial leads (V₁-V₃) and an incomplete or complete RBBB. SCD is caused by polymorphic VT and/or ventricular fibrillation (VF). BS is thought to be responsible for 4% to 12% of all SCD and for up to 20% of SCD in subjects without structural heart disease. Since the ECG is dynamic and often concealed, it is difficult to estimate the real prevalence of the disease in the general population. The prevalence of BS is estimated at 1-5 per 10,000 inhabitants worldwide. It is less frequent in western countries and higher (>5 per 10,000) in Southeast Asia, especially in Thailand and the Philippines where BS is considered to be the major cause of natural death in young individuals.

**Genetic Aspects**

The first mutation related to the syndrome was described in 1998 by Chen et al and was identified in the gene SCN5A that encodes the α-subunit of the cardiac sodium channel. Mutations in the SCN5A gene are presently found in 18%-30% of patients with BS. Inheritance in BS occurs via an autosomal dominant mode of transmission. To date, 293 other mutations have been found in the same gene. In 2002, Weiss et al described a second locus on chromosome 3, which was not linked to SCN5A: the gene identified was the glycerol-3-phosphate dehydrogenase 1-like (GPD1L) gene. Mutations in the GPD1L gene, which codes an enzyme regulating the trafficking of the cardiac sodium channel to the cell surface, have
been shown to reduce inward sodium currents by approximately 50%. Recently, mutations in the CACNA1c and CACNB2b genes, which code for calcium channels, and in the KCNE3 gene, which codes for a subunit regulating the Ito potassium current, have also been shown to be responsible for the BS phenotype.

A BS ECG is not the only phenotype linked to mutations in the SCN5A gene. Recent evidence indicates a lot of overlap in clinical presentation (“overlapping syndromes”). The most frequently reported overlap is the concomitant presentation of BS and cardiac conduction disease (Lev-Lenegre disease, sick sinus node syndrome). The overlap between the LQT3 and BS phenotypes has also been reported in several cases. In recent years, the association of atrial fibrillation with known sodium channelopathies such as BS, progressive cardiac conduction disease, LQT3 and short QT syndromes has been also reported. Interestingly, atrial fibrillation has been shown to be potentially the first phenotypic expression of a latent form of BS which manifests only years later.

**Pathophysiology**

Two main hypotheses have been proposed to explain the pathophysiologic mechanisms of ECG abnormalities and susceptibility to VAs in patients with BS. In 1999, the theory of “impaired repolarization” was proposed. This theory was based on a non-homogeneous expression of the transient outward potassium current (Ito) between epicardium and endocardium. Ito, which is responsible for the early repolarization phase during action potential (AP), is more strongly expressed in the epicardium. In the presence of a loss or reduced function of the sodium channels, a “spike and dome” AP shape arises. The effect on the action potential will be more evident in the epicardium layer, where the Ito is stronger. Thus, a discrepancy in the AP shape between endocardium and epicardium will result in the surface BS ECG patterns. Abnormalities in the surface ECG will be proportional to the discrepancy in the AP, creating slight ECG alterations (saddle-back ST elevation, J point <0.2 mv) or marked ECG alterations (cove type, J point >0.2 mv) according to the degree of sodium channel damage and the different Ito expression. The conduction of the AP dome from sites where it is maintained to sites where it is lost provokes local re-excitation via a phase 2 reentry mechanism with a closely coupled extrasystole occurring during the vulnerable period. These PVC may then trigger malignant VAs.

The second theory, called “depolarization theory,” is based on the presence of conduction delay in the RVOT. According to this theory, the AP shape is maintained, but the RVOT AP is delayed with respect to the RV AP. These AP timing differences in adjacent areas of myocardium may be a source of reentry circuits triggered by PVC originating in the border zone between early and delayed depolarization.

A third theory, based on the abnormal expression of the neural crest on myocardial development of the RVOT and surrounding structures, has been recently proposed by Elizari et al. During embryogenesis, the cardiac neural crest plays a critical role in morphogenesis of the RVOT, which comprises the free wall and the aorto-pulmonary septum, and the great arteries. A population of cardiac neural crest cells migrates toward the arterial pole of embryonic heart leading to myocardial cell proliferation, differentiation and RVOT myocardialization. A second population of migratory cardiac neural crest cells enters the heart via the venous pole and plays a crucial role in the formation of the AV node, the His bundle, the beginning of the bundle branches, and atrial tissue.

Consequently, abnormalities in right heart formation related to the cresta neuralis from outside the heart could explain all of the electrical abnormalities (supraventricular arrhythmias, conduction disturbances, ventricular arrhythmias) potentially manifesting in patients with BS and the overlapping syndromes.

In particular, a non-homogeneous expression of connexins, molecules which are highly expressed by neural crest cells, may be responsible for the erroneous migration of neural crest cells toward the embryonic heart. Mistiming of neural crest cell migration due to a connexins malfunction may have a deleterious effect on cardiac tissue remodeling of RV. Thus, abnormal RVOT myocardialization which depends on neural crest cell migration might explain the repolarization heterogeneities underlying the BS phenotype. This model hypothesizes an unequal distribution of repolarizing forces. According to this theory, repolarization gradients causing ST-segment elevation occur not only between the epicardium and endocardium (because of higher Ito expression in epicardium than in endocardium) but also between RVOT and normal surrounding structures.

**Clinical Presentation**

The clinical presentation in patients with BS can range from a complete lack of symptoms to sudden death. Syncope, seizures, palpitations, and nocturnal agonal respiration have all been described.
from $V_1$ and $V_2$ leads at higher (3rd and 2nd) intercostal spaces increase the sensitivity and specificity of the ECG diagnosis for the Brugada phenotype.\cite{76,77}

Consequently, according to the Second Consensus Conference criteria, BS is diagnosed when a type 1 ST-segment elevation is observed in >1 right precordial leads ($V_1$-$V_3$) in the presence or absence of a sodium channel-blocking agent and in conjunction with one of the following events: documented ventricular fibrillation, (self-terminating) polymorphic VT, a family history of SCD under the age of 45 years, presence of coved-type ECG in family members, inducibility of VT with programmed electrical stimulation or syncope. Patients displaying the characteristic coved-type ECG pattern without further clinical criteria should be considered as having a Brugada ECG pattern and not a BS. Very recently, we have shown that a type I ECG in one precordial lead is sufficient for the diagnosis.\cite{78}

All the 3 patterns described above may be observed spontaneously in serial ECG tracings from the same patient, as well as “pseudo-normalization” of the ECG.\cite{79} In clinical practice, these ECG fluctuations can make it quite difficult to identify individuals affected by BS and at risk for SCD. In addition to sodium channel blockers, many agents and conditions are reported to unmask a type 1 BS ECG phenotype, including body temperature, changes in autonomic tone and drugs affecting ion channel function, such as calcium-channel blockers, beta-blockers, antiarrhythmic drugs, psychotropic agents, and even some hormones.\cite{66}

BS is mainly considered an arrhythmogenic disease of adult males (80%), with a reported mean age at sudden death of 40 years.\cite{71} Clinical studies suggest that the male hormone, testosterone, may be responsible for the gender differences observed in the prevalence of BS.\cite{72-74}

**ECG and Clinical Characteristics**

According to the Second Consensus Conference on BS, 3 ECG repolarization patterns are currently recognized, (Figure 6). Type 1, which is the only one diagnostic of BS, is characterized by a coved ST-segment elevation ≥2 mm (0.2 mV) followed by a negative or flat T wave. The type 2 ECG repolarization pattern is characterized by ST-segment elevation, which has a “saddleback” appearance with a high takeoff ST-segment elevation of ≥2 mm and either positive or biphasic T wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. Type 2 and 3 are not diagnostic for BS, but the diagnosis of BS is also considered positive when a type 2 or 3 pattern is observed in >1 right precordial lead under baseline conditions and conversion to the diagnostic type 1 pattern occurs after sodium channel blocker administration.\cite{75} ECG recordings from $V_1$ and $V_2$ leads at higher (3rd and 2nd) intercostal spaces increase the sensitivity and specificity of the ECG diagnosis for the Brugada phenotype.\cite{76,77}

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drugs and alcohol or cocaine toxicity. Recently, Amin et al showed that exercise, especially during the recovery phase, is also able to unmask a type 1 BS-ECG or to increase the precordial peak J point elevation.  

Diagnostic Tools: the Class I Antiarrhythmic Drugs Challenge

Given that the ECG is dynamic and that the characteristic ECG hallmark may thus be concealed, drug challenge with sodium channel blockers that increase the sodium channel dysfunction has been proposed as a useful tool for the diagnosis of BS. Currently, ajmaline, administered as an intra-venous dose of 1 mg/kg over 5 minutes, represents the first choice due to its high sensitivity and specificity in identifying gene carriers (80% and 94.5% respectively). Additionally, the short half-life and brief duration of its electrophysiological effects render it safer than other antiarrhythmic drugs.

Risk Stratification

The presence of a spontaneous right precordial ST segment elevation (coved type), history of clinical symptoms (syncope, aborted sudden death), and male sex are risk factors for malignant clinical events in patients with BS. There is general agreement that survivors of cardiac arrest have a high risk of recurrent life-threatening arrhythmic events and should therefore receive an ICD. Previous syncope may be reported in up to 23% of patients who experience an episode of cardiac arrest. Neurally mediated syncope has also recently been associated with BS, but its implications for prognosis and risk stratification are still unknown. Males have consistently shown a tendency to present more arrhythmic events in all studies, and being male was identified as an independent predictor for poorer outcome in a recent meta-analysis. The best management approach in asymptomatic patients and whether electrophysiological studies are useful or not in predicting adverse events is still controversial.

Treatment

The only proven therapy to prevent sudden death in symptomatic Brugada patients is an ICD. Quinidine can be used as a pharmacological therapeutic option. Its use might be particularly useful in patients with an ICD and multiple shocks and as an initial therapeutic option in young patients at high risk for malignant arrhythmias. However, real scientific data on its efficacy are still lacking.

RIGHT VENTRICULAR OUTFLOW TRACT VENTRICULAR TACHYCARDIA

RVOT VTs are the most common form of idiopathic VTs. In most cases (70%-80%), RVOT VT does actually originate in the RVOT; however, other origins are possible, including the septum, the left ventricular outflow tract, the pulmonary artery, the aortic sinus of Valsalva, the area near the His bundle, and the epicardial surface of the ventricles. The characteristic morphology of the RVOT-VT is a wide QRS complex tachycardia with LBBB morphology and an inferior axis (Figure 7). Ventricular tachycardia is monomorphic and generally not familial.

Clinical presentation of RVOT-VT is variable and symptoms usually occur from the third to the fifth decade of life. RVOT-VT occurs more frequently in women. Two phenotypic forms of RVOT-VT are known: exercise or stress-induced sustained VT and nonsustained, repetitive monomorphic VT at rest. Both forms are characterized by adenosine sensitivity. Nonsustained VT, which usually occurs as repetitive runs of monomorphic VT, is frequent comprising 60%-92% of reported series. Most patients present with palpitations or presyncope, and rarely present with syncope. Exercise or emotional stress usually precipitates the tachycardia. Resting ECGs in these patients show no identifiable abnormalities. Echocardiogram and coronary angiography are normal in most of the patients. The MRI may show abnormalities in up to 70% of patients, including focal thinning, diminished wall thickening, and abnormal wall motion. However, the real meaning of these “abnormalities” is not known.

RVOT-VT shows a benign course, suggesting that, in the majority of cases, this arrhythmia is not a first form of an occult cardiomyopathy. Gaita et al reported that 61 patients with RVOT ventricular extrasystoles were contacted 15 years after the initial visit but found that no patients had died of SCD or developed ARVD in the study.

However, some authors have reported that “malignant arrhythmias” such as ventricular fibrillation and/or polymorphic VTs, are sometimes associated with idiopathic VT or PVC originating in the RVOT. Patients potentially at high risk for this “malignant” variant appear to be those with: a) a history of syncope; b) very fast VT (heart rate >230 bpm); c) PVC with a short coupling interval; and d) long average QRS duration of the initiating PVC originating from the RVOT. Catheter ablation should be strongly considered for patients with the latter characteristics.

In the differential diagnosis ARVD should be strongly suspected and investigated.
Treatment

The management strategy for RVOT-VT includes antiarrhythmic drugs and catheter ablation. If symptoms are very mild or infrequent, no treatment is necessary. RVOT-VT can be arrested acutely by vagal manoeuvres, carotid sinus massage, intravenous adenosine (6-18 mg), and intravenous verapamil (5-10 mg). Efficacy of antiarrhythmic drugs (beta-blockers, calcium channel blockers) in patients with RVOT-VT is around 25%-50%. Considering the long-term success rate (>90%) and the low incidence of major complications (<1%), catheter ablation is becoming the first-line therapy in patients with RVOT-VT.

CONGENITAL HEART DEFECTS (TETRALOGY OF FALLOT)

Rhythm disturbances may be observed in the natural history of congenital heart defects (CHD), as well as after open heart surgery. An increasing number of patients with CHD are reaching adulthood, due to the success of corrective surgical procedures. About 40%-50% of adults with CHD will experience some type of arrhythmia. The high incidence of cardiac arrhythmias in the adult with CHD can be caused by abnormal pressure/volume changes and more often by re-entrant circuits created by septal patches and suture lines. Supraventricular tachycardias, such as atrial flutter...
and/or atrial fibrillation, are common in CHD (Figure 9).

VT is seen in a smaller number of patients, most notably in those with tetralogy of Fallot (TOF). This condition consists of four features: subpulmonary infundibular stenosis, ventricular septal defect, overriding aorta, and right ventricular hypertrophy. The surgical procedure includes a right ventriculotomy and ventricular septal defect patch repair. These lesions cause the arrhythmia substrate. The ventricular septal defect patch repair provides a fixed anatomic obstacle around which re-entrant arrhythmias may occur.

After repair of TOF, sustained VT has a prevalence of 4%-7% and is usually a RVOT reentrant tachycardia with LBBB morphology. Nonsustained VAs are present in up to 60% of Holter recordings.

In these patients, there is a persistent risk of late SCD, with an estimated incidence rate of 0.5%-8.3%. Older age at initial repair, moderate or severe pulmonary regurgitation, a history of sustained VT, moderate or severe ventricular dysfunction and a QRS duration ≥180 ms are predictive of risk of SCD. Nonsustained VT in patients with TOF has shown no predictive value for subsequent sustained VT or SCD. The patients usually present with palpitations, less often with syncope or presyncope. Antiarrhythmic drugs such as amiodarone and sotalol are usually used in these patients as first-line therapy. In patients with drug-refractory symptomatic VT, radiofrequency ablation can be performed. Conventional and electroanatomical mapping are used to identify the reentry circuit. Electroanatomical mapping may be crucial for success, especially in poorly tolerated VTs. An isthmus between an area of anterior wall RVOT scar/patch and the tricuspid annulus (Figure 10) has been shown to be the main cause of VTs (75%) in symptomatic patients undergoing radiofrequency ablation after repair of TOF. Long-term success can be achieved in about 90% of patients. An ICD is indicated in patients with aborted SCD and VT which cannot be ablated.

Right Ventricle, ECG Abnormalities, and Sudden Cardiac Death in Athletes

It has been estimated that VAs in right ventricular disease such as BS and ARVD account for 10%-30% of SCD in young adults in the general population. This percentage is even higher in young athletes. Spain has recently suffered a plague of sudden deaths among young national soccer players affected by ARVD. It has been reported that 20-35 young athletes die
suddenly in Spain each year. In young, otherwise apparently healthy subjects, SCD is always a tragic event and can be even crueler when photographed for viewing by millions of people. Pre-participation screening has been shown to decrease SCD among athletes.\textsuperscript{111} Abnormal 12-lead ECG in trained individuals are frequent. Common and training-related abnormalities include sinus bradycardia, first degree and Wenckebach heart blocks, incomplete RBBB, left ventricular hypertrophy and an early repolarization pattern. These physiologic abnormalities reflect the remodelling of the heart and the change in autonomic balance in individuals who train regularly and intensely. However, in a small percentage of cases (8\%),\textsuperscript{112} ECG changes may be marked and diffuse. A careful interpretation and investigation (Figure 11) is required in these cases to rule out life-threatening disease, especially in presence of syncoes and/or a family history of SCD. Cardiac genetic disorders (ARVD, BS, hypertrophic cardiomyopathy, long-short QT syndrome) have varying levels of environmental contribution that can worsen or even unmask the phenotypic expression of the disease. In patients with ARVD, exercise accelerates the genetically determined damage of mechanical contacts.\textsuperscript{113,114} Exercise, especially during the recovery phase, is also able to unmask a type 1 BS-ECG and consequently to expose the subjects to life-threatening conditions.\textsuperscript{81,115-117} In general, patients with ARVD and BS should be advised against strenuous exercise and vigorous training and should be excluded from participation in competitive or professional athletic sports.

ICD implantation should be seriously considered after a careful risk stratification. Debate exists as to whether athletes who have received an ICD may or may not continue competitive sports. According to the Bethesda guidelines,\textsuperscript{118} patients with an ICD can participate only in “class IA” activities, such as bowling or golf. Conversely, more recent data showed that, although shocks during sports are reported frequently, significant adverse events are rare.\textsuperscript{119} Therefore, physician recommendations regarding participation in sports still vary widely. Several theoretical and practical reasons exist to restrict athletes with ICDs from participation in sports but data actually proving sports to be dangerous for all ICD patients are not available and an informed decision should probably lie with the individual athlete.

REFERENCES


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**Figure 10.** Localization of anatomic boundaries (blue line) for right ventricular tachycardia after repair of cardiac heart defect and the resulting anatomic isthmuses (red lines, numbers from 1 to 4). RV indicates right ventricle; RVOT, right ventricular outflow tract; TA, tricuspid annulus; VSD, ventricular septal defect. Modified from Zeppenfeld K et al. with permission.

**Figure 11.** The ECG is from an asymptomatic 17-year-old competitive soccer player at rest without evidence of left ventricular hypertrophy or other structural abnormalities on echocardiography. The ECG shows marked repolarization abnormalities, including ST-segment elevation and T wave inversion in precordial lead V1-V4. With this ECG pattern the exclusion of life-threatening cardiac conditions such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, dilated cardiomyopathy, aortic valve stenosis, and channelopathies (Brugada syndrome, long and short QT syndrome) is mandatory.


104. Albert CM, Mittelman MA, Chae CU, Lee IM, Hennkens CH, Manson JE. Triggering of sudden death from cardiac...