Arrhythmogenic Right Ventricular Cardiomyopathy
A Challenging Disease of the Intercalated Disc

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Clinical Case
A 52-year-old male patient, a former competitive athlete, was admitted to the hospital because of recurrent episodes of palpitations and presyncope, which occurred while he was running in the course of the previous 12 months. Family history was significant for a first-degree cousin who received an implantable cardioverter-defibrillator (ICD) at 38 years of age because of an unclassified cardiomyopathy. An initial resting 12-lead ECG showed sinus rhythm at a heart rate of 57 beats per minute with an atypical right bundle-branch block, extensive notching of the QRS complex in leads V1 to V3, visible late potentials (resembling epsilon waves) in the inferolateral leads, T-wave inversions in leads V1 to V4, and one ventricular beat with left bundle-branch block morphology and superior axis as well (Figure 1, top). Exercise testing induced a sustained ventricular tachycardia (VT) at a rate of 200 beats per minute with left bundle-branch block morphology and superior axis (Figure 1, bottom) at a rate of 230 beats per minute. Electroanatomic voltage mapping demonstrated low-voltage areas and scar within the RV corresponding to the regional wall motion abnormalities (Figure 3). Endomyocardial biopsies taken from the RV septum revealed some fibrotic infiltration surrounding the myocytes. Genetic testing yielded a severe heterozygous mutation of desmoplakin at position E1181, resulting in a premature stop codon and truncation of the protein desmoplakin.

Background
Arrhythmogenic cardiomyopathy, as recently renamed by the Heart Rhythm Society/European Heart Rhythm Association consensus statement, was first described as arrhythmogenic right ventricular dysplasia and later increasingly referred to as arrhythmogenic right ventricular cardiomyopathy (ARVC). It constitutes a polygenic myocardial disease with a predominantly autosomal-dominant inheritance pattern. Progressive ventricular myocyte loss and replacement by fibrous and adipose tissue are pathological hallmarks of the disease. In later stages, the LV can also be involved, which is often associated with an unfavorable prognosis.

Genetics
Molecular studies have identified causative genetic mutations, mainly affecting proteins of the intercalated disc, particularly the desmosome, a large intercellular junctional protein...
complex responsible for the mechanical coupling of myocytes (Figure 4). It is suggested that up to 60% of ARVC cases are familial, but disease penetrance is incomplete.

Epidemiology
ARVC commonly manifests during adolescence with a prevalence of 1:1000 to 1:5000. Ventricular arrhythmias are often a first manifestation of ARVC, and the proportion of ARVC as the cause of sudden cardiac death (SCD) in victims <30 years of age has been estimated to be up to 25%.

Pathology
Extensive fibrofatty infiltration and myocardial atrophy are hallmarks of ARVC. Very thin regions, typically located in the so-called triangle of dysplasia (Figure 3)—subtricuspidal region, RV outflow tract, and RV infero-apical region—are particularly prone to ventricular aneurysm formation.

Pathogenesis
Genetically determined disruption of the integrity of the intercalated disc is the key factor promoting ARVC, named as the defective desmosome hypothesis. The 3 current theories for the progressive fibrofatty replacement of the myocardium include (1) myocyte apoptosis/necrosis following the disruption of the intercalated disc, (2) inflammation, and (3) transdifferentiation of myocytes.

Diagnosis
Revised 2010 Task Force Criteria
Currently, no gold standard exists to establish or exclude ARVC. In 2010, the original 1994 Task Force Criteria were revised by Marcus and colleagues. The importance of pathogenic mutations for ARVC was acknowledged, and precise cutoff values for

Figure 1. Top, Twelve-lead baseline ECG showing sinus rhythm with an atypical right bundle-branch block, extensive notching of the QRS complex in leads V1 to V4 (arrowhead), parietal block (QRS duration in V1–V3 that exceeds the QRS duration in lead V6 by >25 ms), late potentials in the inferolateral leads (thin arrows), T-wave inversions in V1 to V4, and 1 with left bundle branch block morphology and superior axis premature ventricular beat (bold arrow). Bottom, A nonsustained VT with LBBB morphology and superior axis (negative QRS in leads II, III, and aVF and positive in lead aVL) at a rate of 230 beats per minute was induced during an electrophysiological study, a major criterion for ARVC according to the Revised 2010 Task Force Criteria. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; LBBB, left bundle-branch block; and VT, ventricular tachycardia.
imaging/histology were provided. The Revised 2010 Task Force Criteria assign 6 categories, as follows: (1) global and regional myocardial dysfunction and structural abnormalities, (2) histological characterization, (3) depolarization abnormalities, (4) repolarization abnormalities, (5) ventricular arrhythmias, and (6) family history and genetic testing. Definitive diagnosis requires 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria from different categories. ARVC is considered borderline, if 1 major and 1 minor criterion or 3 minor criteria are present. ARVC is possible, if 1 major criterion or 2 minor criteria are present.

**Diagnostic Workup**

**Physical Examination**

Fifty percent of patients will have an unremarkable physical examination. The other 50% will show abnormalities such as giant a waves on the jugular veins, a tricuspid regurgitation murmur, a fixed splitting of S2, and right-sided S3 to S4 at the left sternal border with augmentation during inspiration.

**Twelve-Lead ECG and Signal-Averaged ECG**

An abnormal 12-lead surface ECG will be present in ≈50% of patients. Of note, dynamic ECG changes are not uncommon and may reflect subtle disease progression. Typical abnormalities include pathognomonic epsilon waves (defined as distinct waves of small amplitude that occupy the ST segment in the right precordial leads and are distinct from the QRS complex), a QRS duration of ≥110 ms, and T-wave inversions in V1 to V3 and beyond. Yet, T-wave inversions in V1 to V3 may potentially be benign, even after puberty. A prolonged S-wave upstroke in V1 to V3 of ≥55 ms is considered as a minor criterion for ARVC. Signal-averaged ECG is considered as an important tool to indirectly quantify anatomic damage.

**Stress Testing**

Exercise testing can provoke ventricular arrhythmias and can help to exclude ischemic heart disease.

**TTE, CMR, and RV Angiography**

TTE remains the initial imaging tool in patients with suspected ARVC and for family member screening. It may demonstrate RV enlargement and regional contraction abnormalities. The LV can also be affected, displaying regional hypokinesis, late gadolinium enhancement, and reduced ejection fraction. LV structural abnormalities are often localized in the apical and lateral region. CMR has emerged as the noninvasive diagnostic tool of choice for assessing the RV. It may also reveal intramyocardial fibrofatty infiltration, although these parameters were not integrated in the Revised 2010 Task Force Criteria because of limited specificity and high intra/interobserver variability. RV angiography may be useful to diagnose ARVC if the diagnosis remains uncertain (www.arvd.org). The stepwise approach of using TTE, CMR, and RV angiography increases the diagnostic yield. The clinician should be aware that ARVC cannot be excluded by the absence of structural abnormalities at initial examination, because arrhythmias often occur in the concealed phase without structural abnormalities, which may evolve years later. Genetic testing may help to identify ARVC in this early setting.

**EP Study and Electroanatomic Voltage Mapping**

Clinical arrhythmias may be induced during an EP study, although the role of EP study for risk stratification remains controversial. Yet, reproduction of clinical VT can guide ablation. Electroanatomic voltage mapping is a technique that uses standard diagnostic EP catheters to measure local...
voltages of the myocardium (Figure 3). Fibrofatty tissue and scar translates into low voltages with a longer duration and fractionation of signals.

**Endomyocardial Biopsy**

Endomyocardial biopsy may help to exclude differential diagnoses such as sarcoidosis or giant cell myocarditis. However, the septum is often spared by significant fibrofatty infiltration. Thus, negative biopsies cannot exclude ARVC because of the intrinsic problem of sampling error. To increase the yield, several biopsies should be obtained with expert care, because thinned regions carry an increased risk of perforation. Immunohistochemical analysis of proteins from the intercalated disc may serve as an additional valuable tool for confirming the diagnosis in selected patients.³

**Genetic Testing**

The Heart Rhythm Society/European Heart Rhythm Association has published a consensus statement regarding genetic testing in ARVC. Genetic testing is performed to establish a conclusive diagnosis in probands with an intermediate to high clinical suspicion of ARVC and to identify genetically affected relatives. It is not recommended in probands fulfilling only 1 minor criterion. Of note, genetic testing may only support a clinical diagnosis, and a negative test cannot rule out ARVC.

**Differential Diagnosis**

Idiopathic RV outflow tract–VT is a mostly benign condition not associated with structural heart disease and must be considered in differential diagnosis. Myocarditis may be excluded by genetic testing, electroanatomic voltage mapping, and endomyocardial biopsy.¹³ Cardiac sarcoidosis has to be considered, if respiratory or systemic symptoms or a high-grade atrioventricular block are present. Dilative cardiomyopathy may be difficult to distinguish from nonclassic forms of ARVC, although it usually first presents with symptoms of heart failure rather than ventricular arrhythmias. Electrocardiographic abnormalities in Brugada syndrome may be similar to those in ARVC, because conduction delay within the RV outflow tract has also been demonstrated in this syndrome.

Figure 3. Electroanatomic voltage mapping demonstrated low-voltages areas (bipolar <1.5 mV, blue) and scar (bipolar <0.5 mV, red) within the triangle of dysplasia (see text), corresponding to the regional wall motion abnormalities.

Figure 4. Schematic illustration of the intercalated disc with the desmosome as its key component (left), an important cellular structure providing cell–cell adhesion and mechanical integrity within the heart muscle. The enlarged sector (right) schematizes the desmosomal network and its major components. Abnormalities within this network may cause ARVC. ARVC indicates arrhythmogenic right ventricular cardiomyopathy.
Risk Stratification and Prognosis
Risk factors for SCD in ARVC include the following: (1) previous aborted SCD, (2) documented VT/ventricular fibrillation, (3) patients with previous syncpe, (4) LV dysfunction, (5) RV dilatation/dysfunction or severe tricuspid regurgitation, and (6) symptom onset at <35 years of age (triangle of risk).14,16 Yet, the individual disease course is very variable, as demonstrated in a recent study with a mean life expectancy of 54 years of age. Most patients die of progressive heart failure or SCD.15

Therapy
Physical Activity Restriction
Previous studies in animals and humans have suggested that increased RV preload during training periods contributes to the accelerated expression of ARVC, rapid disease progression, and occurrence of ventricular arrhythmias in patients carrying genetic variations conferring an impaired stability of the intercalated disc, which is probably related to overexpansion by increased shear forces during exercise.16 Of note, young competitive athletes with ARVC have a 5- to 6-fold increased risk of SCD in comparison with nonathletes. Thus, strenuous physical activity, particularly competitive sports, should be discouraged.

Pharmacological Therapy
Amiodarone or sotalol can both be effective for treatment of sustained VT/ventricular fibrillation in ARVC.17 However, neither has a proven prognostic benefit. Recent data from the North American ARVC registry demonstrated that amiodarone confers the greatest efficacy in preventing ventricular arrhythmias in comparison with sotalol or β-blockers.18 If heart failure occurs, standard therapy with a β-blocker, an angiotensin-converting enzyme inhibitor, and a diuretic should be established.

Implantable Cardioverter-Defibrillator
ICD therapy is the cornerstone for ARVC patients at moderate to high risk for SCD and can prolong survival in this population,19 whereas, in low-risk patients, its role is less well established. Thus, in each patient in whom ICD implantation is considered for primary prophylaxis, the individual lifelong risk for lethal arrhythmias has to be weighed against the complication rates.

Catheter Ablation
Catheter ablation of VT is a palliative intervention owing to multiple reentry circuits and epicardial involvement. Currently accepted indications include drug-refractory VT or incessant VT with frequent ICD shocks. Contemporary mapping and ablation techniques combining an endocardial and epicardial approach appear promising with respect to safety, arrhythmia-free survival, and reduction of ICD discharges.20

Case Resolution
Having established a diagnosis of definite ARVC with 3 major (reduced RV ejection fraction and regional RV dyskinesis, VT with left bundle-branch block morphology and superior axis, and a pathogenic mutation) and 1 minor criterion (T-wave inversions V1–V4), and a high risk for SCD (spontaneous symptomatic sustained VT, syncpe, extensive RV disease, LV involvement), a dual-chamber ICD was implanted. Furthermore, a β-blocker was started, and restriction from strenuous physical exercise was strongly recommended. Since last-follow up, the patient has been asymptomatic. Family screening was recommended for the primary- and secondary-degree relatives. Lifelong follow-up is warranted for our index patient and his primary-degree relatives.

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None.

References


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