

# The Electrocardiographic Manifestations of Arrhythmogenic Right Ventricular Dysplasia

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**Abstract:** The ECG is abnormal in most patients with arrhythmogenic right ventricular dysplasia (ARVD). Right ventricular parietal block, reduced QRS amplitude, epsilon wave, T wave inversion in VI-3 and ventricular tachycardia in the morphology of left bundle branch block are the characteristic changes that reflect the underlying genetic predetermined pathology and pathoelectrophysiology. Recognizing the characteristic ECG changes in ARVD will be of help in making a correct diagnosis of this rare disease.

**Keywords:** ECG, ARVD, desmosomal genes, ventricular tachyarrhythmia, SCD.

## INTRODUCTION

The electrocardiogram (ECG) is the most commonly used test in cardiology. In this era of high technology and evidence-based medicine of the 21<sup>st</sup> century, the fundamentals of ECG applications in the diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) still remain unshakable.

Since the beginning recognition of ARVD, [1-4] it is now appreciated as a genetic arrhythmogenic cardiomyopathy associated with an increased risk of sudden cardiac death (SCD). The pathology is characterized by the gradual loss of myocardium with fatty or fibrofatty tissue replacement, predominantly affecting the right ventricle and resulting in regional and global myocardial dysfunction. Areas of slow conduction and disparate refractoriness set the stage for reentrant ventricular tachyarrhythmias. ARVD development is mostly a concealed process in its early stages. Thus, SCD can be the first symptom occurring in young, apparently healthy individuals and endurance athletes. High risk individuals often experience the so-called 'hot phase' of the disease [5] featuring recurrent malignant ventricular tachyarrhythmias, whereas low risk individuals may have an uneventful clinical course. Because of the disease progression, congestive biventricular failure is the main cause of death and heart transplant may be required at the end stage of the disease [6, 7].

## GENETIC BASIS AND THE PATHOGENESIS OF ARVD

Like many other familial disorders, there is a high degree of genetic heterogeneity in ARVD. To date, mutations of over 12 genes have been identified that can cause ARVD, or result in an ARVD phenotype, although some of these gene

are also responsible for other diseases. Genes can be sub-grouped into desmosomal and non-desmosomal types. Desmosomal genes are *JUP* encoding plakoglobin, [8-11] *DSP* for desmoplakin [12], *PKP2*, plakophilin-2 [13-15], *PKP4*, plakophilin-4 [16], *DSG*, desmoglein-2 [17, 18], and *DSC2* for desmocollin-2 [19, 20]. Non-desmosomal genes are: *TMEM43* [21] containing a response element for peroxisome proliferator-activated receptor gamma (PPAR-gamma), which is an adipogenic transcription factor regulating adipogenic pathway; *CTNNA3*, a gene encoding adherens junctional protein alpha-T-catenin [22] that binds plakophilins; and a list of genes that can result in "overlap syndromes" such as *DES* encoding desmin, a major intermediate filament protein interacting with the desmosome. *DES* mutations can cause skeletal myopathies, conduction disorders and an ARVD phenotype [23, 24]. *TTN*, a gene encoding titin expressed in both cardiac and skeletal muscle, is the largest protein in mammals. *TTN* mutations can cause hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), tibial muscular dystrophy and an ARVD phenotype [25]. *PLN*, encoding phospholamban, a Ca<sup>2+</sup>-ATPase regulator involved in assembly and disassembly of the desmosome. *PLN* mutations are associated with both DCM and ARVD [26]. *LMNA*, encoding Lamin A/C the nuclear matrix proteins and mutations of this gene can cause a variable of phenotypes so called 'laminopathies' characterized by alterations in adipose localization and replacement of skeletal myocytes by fibrofatty tissue. With over 100 mutations identified in DCM, *LMNA* is also responsible for ARVD [27]. *RYR2*, the cardiac ryanodine receptor gene mainly accounting for catecholaminergic polymorphic ventricular tachycardia, is linked to ARVD as well [28, 29].

Radical mutations have a high probability of being disease-causing in ARVD [30]. Compound or double heterozygous desmosomal mutations are not rare, and the extent of the disease is high compared to that in single-mutation carriers [13, 30-32]. Among genotyped

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individuals, a *PKP2* mutation is the most common according to multicenter/multinational registry studies [33-39]. In ARVD, the proband often exhibits a severe phenotype whereas reduced penetrance is prevalent among gene carriers [33-39].

The exact mechanism of the causative relationship between mutations in genes encoding both desmosomal and non-desmosomal proteins and the gradual loss of ventricular cardiomyocytes and fatty/fibrofatty replacement predominant in the right ventricle has not been elucidated [40-44]. The reduced desmosomal protein expression shown in endocardial biopsy samples [45] and fat droplet formation within the cardiomyocytes of the diseased hearts observed from histological studies [46, 47] have been replicated recently in *PKP2* mutant induced pluripotent stem cells (iPSCs)-derived cardiomyocytes [48]. The findings from patient specific iPSC-derived cardiomyocytes indicate that the PPAR-gamma pathway and cell metabolic derangement may account for apoptosis and lipogenesis [48]. Moreover, the *PKP2* knockout epicardial progenitor cells have shown adipocyte enlargement and migration, a plausible explanation for fat infiltration predominantly occurred in the right ventricle [43]. The vast majority of genotyped ARVD patients present with autosomal dominant inheritance, although an autosomal recessive pattern has also reported [8-14, 17, 18, 21, 49-51].

Establishing a clinical diagnosis of ARVD is based on a combination of characteristic abnormalities using an updated taskforce scoring system [52] that includes family history, ECG, cardiac imaging, endomyocardial biopsy and the identification of an ARVD-causing gene that can confirm the diagnosis. Since up to 50% of ARVD patients have no mutations in known genes, clinical assessment is essential for a correct diagnosis. A timely diagnosis can facilitate tailored treatment for arrhythmia control [53-55] and for prevention of SCD in high risk individuals using an implantable cardioverter-defibrillators (ICD) [56-60].

Among diagnostic modalities, the ECG is the first test. The vast majority of patients who meet ARVD Task force criteria present with ECG abnormalities, and many studies stress that ECG abnormalities are important elements in ARVD assessment and for family screening. The purpose of this article, therefore, is to describe the common ECG abnormalities associated with ARVD that have been observed by the authors over the years, and by literature review. Recognizing the characteristic ECG changes can increase diagnostic accuracy, and help identify affected members at an early and hopefully pre-symptomatic stage, in a timely and cost effective manner.

## I. ECG IN SINUS RHYTHM

As with any ECG interpretations, the sequence of ECG assessment in ARVD should start from heart rate, rhythm, P-QRS-ST-T morphology, amplitude, duration and axis. Visual inspection may take a few minutes. It is important to observe ECG patterns in all 12 leads. Patient's age, gender, medication and/or device therapy should be taken into consideration during ECG assessment.

## 1. Heart Rate

Based on our observations, the average heart rate in ARVD adults (n= 120, age 39±13 yrs) is within the lower normal range (63±13 bpm). Sinus bradycardia seems more common (37% vs. 20%, p=ns), though the difference did not reach statistical significance when compared with age and gender matched controls. There are case reports of ARVD patients presenting with sick sinus syndrome [61, 62]. Those observations may have been influenced by several factors: 1) sino-atrial involvement during disease progression; 2) some of the ARVD patients were athletes; and 3) use of sotalol, a drug with both beta-blocker and Class III antiarrhythmic effects, commonly prescribed to patients with frequent ventricular tachyarrhythmias [53]. The lower heart rate in ARVD may be of use in differentiating it from acute myocarditis, pericarditis and pulmonary embolism (PE). Although right precordial T wave inversion can be seen in those conditions, they are more likely associated with inappropriate sinus tachycardia. Moreover, the presence of S<sub>1</sub>Q<sub>III</sub>T<sub>III</sub>, defined as a deep or broad S wave in lead I, Q wave and T wave inversion in lead III, is a signature change of acute PE [63-65].

## 2. P Wave

P wave abnormalities are common in ARVD [66]. Notched, widened (P wave duration >110 ms), flat or small peaked P wave are seen in up to 50% of ARVD patients in our study cohort consisting of 120 adults and 20 children. Nevertheless, P wave morphology variations are also found in 37% of age and gender comparable control subjects. Thus presence of P wave abnormalities in ARVD patients may reflect atrial involvement, but they may not necessarily add power to an ARVD diagnosis.

## 3. P-R Interval

A-V conduction delay is common in ARVD [67, 68]. Based on our observations the P-R interval is significantly prolonged in ARVD compared to control subjects (170±32 ms vs 154±21 ms, p <0.0001). First degree A-V block (AVB) (PR interval >200 msec) is seen in 16% of ARVD patients. In our ARVD cohort first degree AVB is seen in 15% of ARVD children, indicating that the conduction system may be involved at the early stage of the disease process. Second and third degree AVB are also reported in ARVD patients [67].

We do need to keep in mind that AVB is also common in patients with right ventricular cardiac sarcoidosis (CS) [69, 70]. The latter is a multisystem granulomatous disorder of unknown etiology. CS can mimic ARVD by ECG presentations, EP study results and even with desmosomal gene expression [71]. Unfortunately, applying the taskforce criteria cannot reliably separate CS from ARVD [72, 75].

## 4. QRS Complex

The regional conduction delay and the loss of myocardium due to ARVD are well reflected in the QRS complex, including changes in duration, morphology and amplitude.

#### 4.1. Regional Prolongation of QRS Duration

Since the first description of right ventricular parietal block [76], localized QRS prolongation in the right precordial leads, such as QRS duration (QRSD) >110 ms, and the terminal S wave prolongation ( $\geq 55$  ms) in V1-3 have been much appreciated as non-invasive indicators of activation delay occurred in the diseased region of the right ventricle [77-82]. Those ECG markers have been factored in the taskforce criteria for ARVD diagnosis [52, 83].

#### 4.2. QRS Fragmentation

A fragmented QRS (fQRS) refers to the 'slurs or notches' appeared on the R or S wave or if the total QRS complex had  $\geq 4$  spikes. fQRS can be a normal variant if it appeared randomly in just a few leads. fQRS presenting in multiple leads is more likely pathologic. The underlying cause is the regional delay in propagation of ventricular depolarization [84]. fQRS is highly prevalent in ARVD patients when applied to amplified and modified ECG recording techniques, including the use of the Fontaine Leads System [85-87]. In real world practice, nevertheless, most ECGs available from ARVD patients and family members were obtained by using standard ECG recording technique. Based on our observations, fQRS is easily recognizable from standard ECGs and they are much more common in ARVD patients (n=140) when compared with 100 control subjects (61% vs 37%,  $p < 0.001$ ). Among them a notch before the end of R or S wave (Fig. 1) is characteristic, seen in 51% of ARVD vs 26% in controls,  $p < 0.0001$ . In ARVD, fQRS is often seen in multiple leads. Such changes, however, are common in CS as well. In the latter, the QRS complex is wider [72]. Since fQRS is also prevalent in other types of cardiomyopathies (both ischemic and non-ischemic) [88, 89], Brugada syndrome [84] and in normal subjects, its use in ARVD diagnosis is limited.

#### 4.3. Reduced QRS Amplitude

We have found that reduced QRS amplitude in  $\geq 6$  leads is seen in 66% of 140 ARVD patients in our study cohort. This feature may be of help in differentiating ARVD from athlete heart. The loss of heart muscle is a major feature in ARVD, and the likely cause of reduced QRS amplitude seen in ARVD patients, especially those in the advanced or late stage of the disease [78, 80]. Since reduced QRS amplitude can be a normal variant or found in many other diseases, its lone use in ARVD diagnosis is limited.

#### 4.4. Poor R Wave Progression (PRWP)

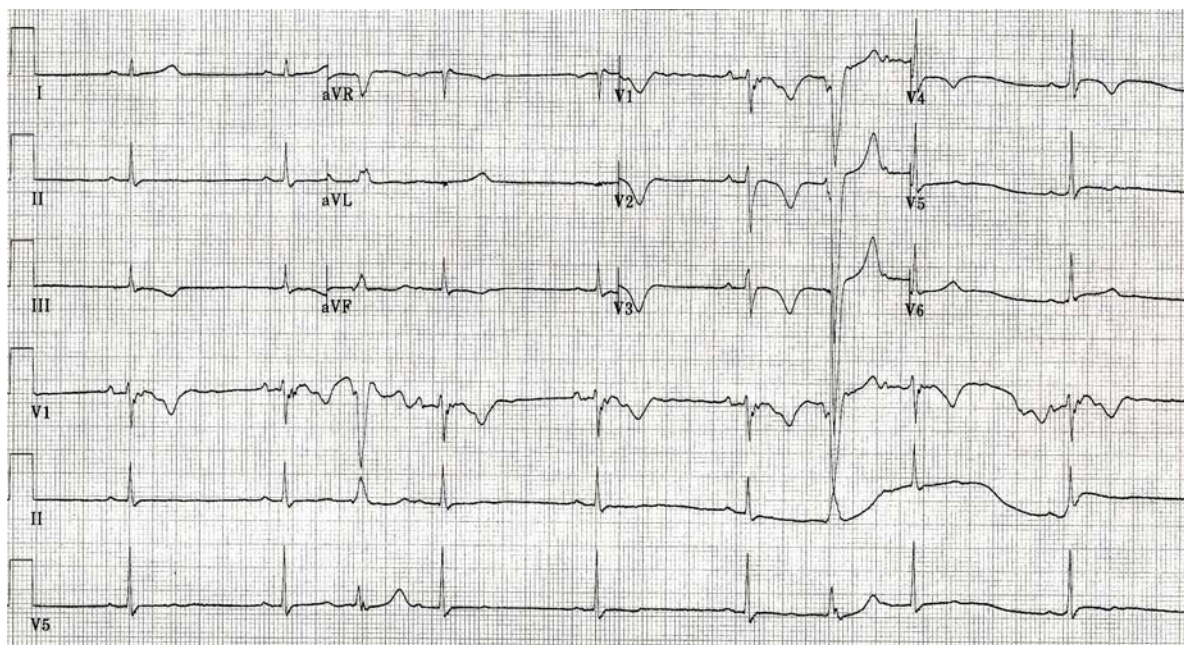
The most prevalent ECG manifestation in ARVD, caused by p.S358L mutation in *TMEM43* gene, is PRWP. Affected males are twice as likely to develop PRWP as affected females [90]. PRWP is also common in other ARVD patients with severe RV dilatation [80]. The most likely cause of PRWP is clockwise rotation caused by RV enlargement.

#### 4.5. QRS Axis

Unlike other types of RV enlargement, left axis deviation is common in ARVD, seen in 22% in our study cohort. Left axis deviation, when associated with left anterior fascicular block, is more common in patients with LV involvement or in the later stages of ARVD [80].

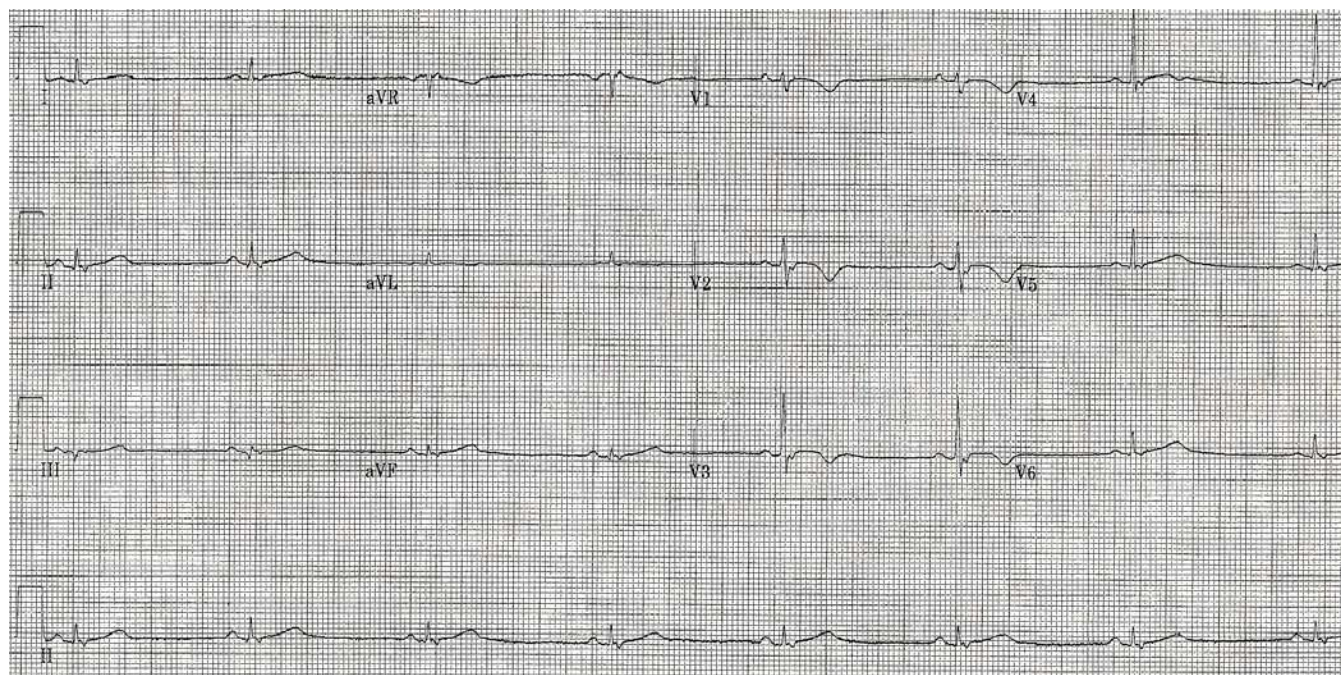
#### 4.6. Right Bundle Branch Block (RBBB)

Complete or incomplete RBBB is common in ARVD [76, 79, 91], indicating that the right heart Purkinje network of the conduction system is impaired. In advanced or later stages, CRBBB is associated with a poor prognosis [92]. CRBBB in ARVD has the following features (Fig. 2): 1) a lower magnitude of both R wave and QRS complex in V1-2; 2) a smaller ratio of R'/S in V1-2; and 3) T wave inversion in V1-3 or beyond is much more common (67% vs. 33%,  $p$



**Fig. (1).** An ECG from a 46-y-old male Caucasian ARVD patient showing 1) sinus bradycardia; 2) interpolated PVCs in LBBB morphology; 3) IRBBB; 4) though there are some artifacts, the terminal S wave prolongation ( $\geq 55$  ms) with a slur, and an epsilon wave that is best appreciated in Lead V1; 4) T wave inversion in V1-4.





**Fig. (2).** ECG from a 41-y-old male ARVD patient showing 1) sinus rhythm and frequent multifoci PVCs and non-sustained VT; 2) Notched P waves in 12 leads; 3) a more than complete RBBB; 4) Characteristic QRS fragmentation including Epsilon waves in both sinus and ectopic beats in 12 leads; 5) Inverted T waves in V1-6.

<0.0001). The rather different looking RBBB morphology seen in ARVD, based on the findings from epicardial mapping and histological data, is likely attributable not only to the impaired bundle branch but also to distal block in the right ventricular wall due to the irregular and delayed propagation of activation in the zones of dysplasia [76]. Therefore, we call it a more than complete (or incomplete) RBBB.

### 5. Epsilon Wave

First reported in 1977 [1], the Epsilon wave is a reflection of ‘mega’ late potentials on the surface ECG that can be seen in patients with advanced or late stage of ARVD [68, 79, 80, 93, 94]. In the diseased region of the right ventricle, the islands of the surviving cardiomyocytes bordered by or embedded in interstitial fibrosis and/or fat causes delayed activation in those areas which results in delayed (late) potentials. Depending on the severity of myocardial damage, the delayed and distort activation may occur before the end of the QRS complex or after the ST segment [1]. Nevertheless, the Epsilon wave is best appreciated in the beginning of the ST segment as small wiggles or a tiny protrusion [1, 87]. Moreover, Epsilon waves are most prominent in the right precordial leads though they can be seen in the limb leads or in all 12 leads (Figs. 2-3). Since the magnitude of the Epsilon wave is generally small, applying Fontaine leads system [87], a very simple method, can amplify Epsilon waves and thereby increase the detection sensitivity significantly [86, 95].

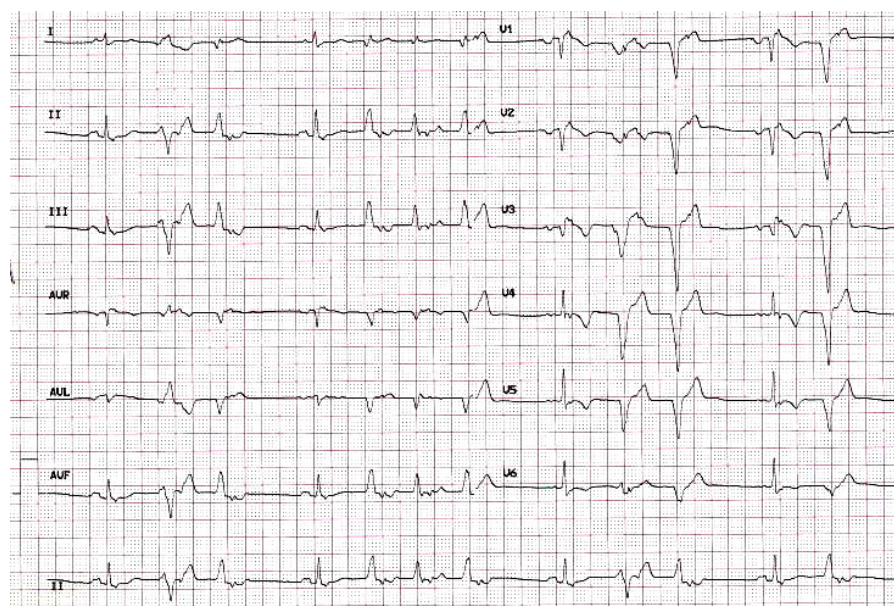
Presence of Epsilon wave is considered as a major diagnostic criterion in ARVD [52, 83] but it is also found in other diseases if late potentials are manifest on the surface ECG [96-101]. For example, Epsilon waves in CS are much more coarse due to extensive formation of fibrosis in the RV [98].

### 6. ST Segment

ST elevation is not uncommon in ARVD [102]. In our study cohort, 37% of ARVD patients had a ST elevation. Among these, 42% showed a small notch (Fig. 1) in the first half of the ST segment and such findings are more frequently seen in patients in the presence of Epsilon waves.

### 7. T Wave Inversion in the Right Precordial Leads

Based on a number of multicenter/multinational studies [3, 78-80, 103, 104], T wave inversion in V1-3 is one of the most common ECG abnormalities in ARVD. Therefore it has been upgraded to a major taskforce diagnostic criterion [52]. In ARVD the regional conduction delay and RV dilatation [80, 105] may be the causes of T wave inversion in V1-3 or beyond. In other words, it is a secondary rather than a primary repolarization abnormality. T wave inversion beyond V3 is more common in ARVD patients in the advanced stage of the disease with severe RV dilatation and LV involvement [80, 106]. Thus it has been considered a risk factor<sup>102</sup> and perhaps an indication of a poor prognosis. T wave inversion in the right precordial leads can also be seen in many other conditions such as acute PE, athlete heart [107-109], Brugada syndrome, long QT syndrome caused by



**Fig. (3).** An endurance athlete first diagnosed with an ‘athlete heart’ for the “unexplained T wave inversion in V1-3” at age 25, and remained asymptomatic until reached age 45, he had a viral infection that initiated the ‘hot phase’ sustained VTs and become very symptomatic. His right heart was significantly dilated by the time of ARVD diagnosis. His arrhythmia was under control by using sotalol, amiodarone and subsequently an ICD. This ECG tracing was taken at age 49, showing 1) marked sinus bradycardia (48 bpm); 2) bizarre QRS complex with evidence of significant conduction distortion and delay in the right ventricle by epsilon waves in all 12 leads; 3) reduced QRS amplitude; 4) Inverted T waves in V1-3.

*KCNH2* mutations or compound mutations, and occasionally in normal adult female.

## II. ARVD-RELATED ARRHYTHMIA

### 1. Atrial Arrhythmia

Atrial extrasystoles, flutter and atrial fibrillation are not uncommon in ARVD [110] especially in those with moderate/severe tricuspid regurgitation and markedly enlarged right ventricles [5, 111, 112]. They can occur prior to or during manifest ventricular arrhythmia [111]. Atrial involvement is a likely cause of these arrhythmias [61, 62].

### 2. Ventricular Arrhythmia

The increased susceptibility to ventricular tachyarrhythmia and SCD is a main feature of ARVD that led to its first recognition in 1977 [1]. Symptoms such as palpitations, dizziness, presyncope and syncope are caused by frequent premature contractions (PVCs), sustained, or non-sustained VT. Since ectopic beats from the ‘triangle of dysplasia’ [3] right ventricular origin is most common, these VTs have a left bundle branch block (LBBB) morphology with superior, inferior or indeterminate axis [52]. VT and PVCs (>500 per 24 hours) in LBBB morphology are considered a minor diagnostic criteria [52]. In many cases VT comes in ‘hot phases’ thus viral infection has been suspected as a prerequisite [113] or a superimposed factor onto ARVD. Drug therapy is empiric. Sotalol or amiodarone in combination with beta-blockers is preferred but their effectiveness is limited due to the nature of the disease [53, 60]. The slow conduction in the diseased region first recorded during epicardial mapping confirmed re-entry as the mechanism of resistant ventricular tachycardia (VT).

This led the pioneer investigators to use aggressive therapeutic approaches such as ventriculotomy [1] and multi-session fulgurations with high energy DC ablation [114, 119]. In recent years, the combined endocardial and epicardial VT ablation incorporating scar de-channeling seems promising in achieving short- and mid-term success [54].

Since ARVD is often a silent cardiomyopathy among affected young people or endurance athletes, and VT degenerating into ventricular fibrillation (VF) is the cause of SCD, ICD therapy is highly effective in cases of aborted SCD and unstable VT, and is recommended to high risk individuals for primary and secondary SCD prevention purposes [56-60].

The differential diagnosis for individuals with recurrent VT with a LBBB morphology is idiopathic right ventricular outflow tract VT (RVOT). The prognosis for these patients is usually benign. Unlike ARVD triggered automatic activity accounts for the vast majority of RVOT VTs [120]. A number of studies have reported the differences in VT morphology between ARVD and ROVT with regard to the duration, fragmentation, frontal axis and the origin of QRS complex [121, 122]. Nevertheless, there is a considerable overlap in VT morphology between these two entities. Sometimes at fast rates, separating the oscillating-like R wave from S wave or the wide QRS complex from T wave is nearly impossible, especially in emergency situations. A careful ECG evaluation in VT and in sinus rhythm is necessary [52, 123, 124].

## III. LATE POTENTIALS

Late potentials refer to the low-amplitude, high-frequency, and altered frequency components in the terminal



QRS complex. They are too small to be visible on the surface ECG tracing. This limitation however was solved by high resolution signal-averaged ECG (SAECG), a summation averaging technique first proposed in 1977 [1] and refined thoroughly over time [125, 126]. The underlying mechanism is all the same regarding late potentials, Epsilon waves, delayed or fragmented electrograms recorded during endomyocardial mapping and the presence of low-voltage areas detected by electroanatomic voltage mapping in the right ventricle of ARVD patients. Presence of late potentials is a minor task force criterion [52]. Utilizing SAECG has shown an improved diagnostic accuracy [127]. In ARVD the prevalence of late potentials is much higher (69%) than that of Epsilon waves in individuals met the taskforce criteria [127]. The prevalence is also higher in ARVD family members (16%), therefore, it can be used for family screenings [128]. In contrast, late potential is mostly negative in RVOT individuals with no apparent structural heart abnormalities [129].

## CONCLUSION

In summary, ARVD is a genetic arrhythmogenic cardiomyopathy associated with an increased risk of SCD. Mutations in both desmosomal and non-desmosomal genes can lead to a gradual loss of myocardium and fatty or fibrofatty replacement predominantly affecting the right ventricle. ARVD development is a concealed process at the early stage. Upon diagnosis, most patients present with ECG abnormalities, indicating the ECG changes may have occurred long before the development of malignant ventricular arrhythmias. ECG abnormalities are characteristic in the majority of patients who meet the task force criteria. Recognizing the common manifestations of ARVD on ECG may help improve diagnostic accuracy. Moreover it can be useful in identifying affected family members. ECG, nevertheless, cannot replace or substitute other diagnostic modalities towards ARVD diagnosis.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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