Overview of Arrhythmias and ECG Changes in ARVC

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Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease of the myocardium predominantly affecting the Right Ventricle (RV) (1, 2). Fibrofatty infiltration of the heart muscle creates repolarisation/depolarisation defects and structural changes predisposing sufferers to potentially life threatening ventricular arrhythmias and heart failure. ARVC, as the name suggests, has traditionally been regarded as a disease primarily of the RV; only affecting the LV at the later stages of the disease as biventricular failure presents. Involvement of the LV is now known to occur much earlier in the disease progression and can occur in isolation. This has lead to a shift towards re-terming this disorder as simply Arrhythmogenic Cardiomyopathy (AC). Pathological changes that present in ARVC are typically described in 4 stages;

- Myocyte loss due to cell apoptosis and necrosis (3)
- Fatty scar forming from the epicardium to endocardium
- RV (and/or LV) wall thinning and chamber dilation
- Aneurysm formation

These changes will ultimately culminate in RV and/or LV dysfunction and may precipitate ventricular arrhythmias (4). In the early stages of the disease process it was believed that any structural changes would be restricted to a region of the RV termed the ‘triangle of dysplasia’ i.e. the inflow tract, outflow tract and apex; these areas were considered particularly vulnerable to aneurysm formation (5, 6).

ARVC is perceived as a disease of the cardiac desmosome as the majority of documented genetic mutations encode for the proteins that form these intercellular electrical and mechanical connections between myocytes. Genetic inheritance of the disease usually follows an autosomal dominant pattern with the exception of the recessively inherited Naxos disease and Caravajal syndrome (6). The broad spectrum of genetic mutations that can cause ARVC means that phenotypic expression is variable. Penetration of the disease is also variable; an individual may have the genetic mutation but never develop the disease.

Clinical manifestations of ARVC typically do not appear until the 2nd to 4th decade despite the genetic mutation being present from birth (7) but can potentially present from the 1st to 8th decade (5). Symptoms associated with ARVC include palpitations, chest pain, syncope and presyncope, but can vary according to the patient’s age and the stage of disease progression, (3). In the earlier stages of the disease structural changes may be minimal (3) and the patient asymptomatic, but despite this they still remain at risk of sudden cardiac death (SCD), especially during exercise. Tragically, cardiac arrest may be the first sign of the disease. ARVC has been found to account for unexplained SCD in 10% of young people (8) and 11-22% of young athletes (1).

Establishing a definitive diagnosis of the ARVC is incredibly challenging for clinicians as the disease can remain concealed, symptoms are non-specific in nature and no single test alone can confirm presence of the disease (2). The priority for diagnosis is early detection of the condition and screening for the relatives of ARVC sufferers. In 1994 the Task force of the European society of Cardiology, Scientific Council on Cardiomyopathies of the International Society and the Federation of Cardiology created a set of criteria for ARVC diagnosis based on medical history, morphological / structural / functional changes, ECG findings, arrhythmias and family history of SCD (2). Whilst these criteria were considered highly specific for ARVC, they lacked the sensitivity required for early detection or family screening and were based on qualitative rather than quantitative data (9). Significant advances in technology, particularly cardiac imaging, and genetics since then are now reflected in the revised 2010 Task Force Criteria (TFC). This comprehensive list of criterion encompasses a range of diagnostic parameters, adopting a quantitative approach, enabling diagnosis to make when only subtle signs of the disease are present and facilitating diagnosis through family screening. Confirmation of ARVC can be confirmed on the basis of 2 major criterions, 1 major and 2 minor or 4 minor criterion.

Arrhythmia in ARVC
Myocardial electrical instability in ARVC can initiate a range of arrhythmias from ventricular extrasystoles to non-sustained or sustained (>30 seconds in duration) VT and ventricular fibrillation (VF) causing SCD (10). The most frequently seen arrhythmia in ARVC is non-sustained or sustained monomorphic ventricular tachycardia (VT) originating from the RV, giving rise to a left bundle branch block (LBBB) morphology (1) with a superior axis (if originating from the apex), and is classified as a major TFC (Figure 1) (3).

Figure 1: Ventricular Tachycardia in a patient with ARVC

In one study, VT with a LBBB morphology was observed in 79% of patients with ARVC and was the first arrhythmia experienced in 39% of this group (11). If the LV is involved, VT can originate from the LV and a right bundle branch morphology will be present (1). VT can also originate from the RVOT and appears with a LBBB and inferior axis but is only listed as minor criteria as idiopathic benign VT commonly arises from this area. Both the benign form of RVOT VT and that resulting from ARVC are seen in young people, present similarly and are often triggered by exercise. It is essential to distinguish between both forms of VT to avoid a false diagnosis of ARVC and ensure appropriate treatment. For example, RVOT VT is more amenable to catheter ablation as its underlying mechanism is one of triggered activity in a focal area (12).

The mechanism of ventricular arrhythmia (VA) in ARVC is commonly scar-related macro re-entry; Fibro-fatty replacement of the myocardium provides the ideal substrate for re-entrant pathways to form (13). Alternatively, triggered activity as, a consequence of Ca++ overload, has been reported in a small percentage of ARVC sufferers who have a genetic mutation in the Ryanodine Receptor and results in VA’s secondary to early or delayed afterdepolarisations (14, 15).

VT will often present during exercise as enhancement of the sympathetic nervous system triggers premature beats and re-entrant pathways (1).

Frequent ventricular ectopics can be observed in nearly a quarter of all ARVC patients, presence of more than 500 during Holter monitoring is classified as a minor criterion in the TFC (3) and unlike non sustained or sustained VT, are not linked with higher rate of mortality (10,11).

Depolarization Abnormalities
Due to fibro-fatty replacement of the RV free-wall, depolarization takes longer which is observed by the presence of epsilon waves and terminal activation delay (TAD) on the ECG and a positive signal-averaged ECG (SAECG).

**Epsilon Wave**

An epsilon wave (arrow Figure 2) is a low-amplitude signal between the end of the QRS and beginning of the T wave [16]. It is the most specific characteristic of ARVC [17] but lacks sensitivity and is generally seen later in the disease course since its presence is associated with a greater degree of RV involvement [16]. It is only observed in between 9-32% of patients with ARVC [19, 20, and 21].

![Figure 2: Epsilon Waves on an ECG and Diagram](image1)

The SAECG is a form of high-resolution electrocardiography, specially adapted to detect small electrical potentials at the end of the QRS complex (late potentials) and localized conduction delay which are difficult to detect using standard ECG techniques. In the diagnosis of ARVC, the TFC require just 1 of the 3 markers to be positive [3]. In this context, the SAECG has a sensitivity of 69% and specificity of 92%. Interestingly, if all 3 of the markers are positive specificity increases to 100%, but sensitivity drops to 33% [22]. The SAECG cannot help predict ventricular arrhythmias (VAs) in ARVC [22].

**Terminal Activation Delay**

TAD is measured from the nadir of the S wave to the end of the QRS complex; this is positive when it exceeds 55ms [20] (Figure 3) and reflects delayed depolarization. Terminal activation delay develops early in the disease process [23], occurring in 90% of ARVC patients with mild or localized disease and in 95% of patients with moderate and severe ARVC, whereas it only occurs in 7% of patients with right ventricular outflow tract ventricular tachycardia and 2% of controls [20].

![Figure 3 – Terminal Activation Delay on an ECG and Diagram](image2)
T wave inversion (TWI) in V1 is a normal variant on a 12-lead ECG. TWI beyond V1 (V1-V3) is also seen in many healthy individuals, most notably in children under the age of 12 years, athletes, Afro-Caribbean’s and women [24]. TWI is a sensitive marker for ARVC which develops early in the condition and, if present in V1-V3 assigns the patient a major point, or a minor point if it only spreads to V2. The TFC team stated that although TWI is seen in ~6% of the healthy population, it is a “reasonably” specific marker for ARVC [25].

In the literature the prevalence of TWI V1-V3 ranges from 40-85% in ARVC [26, 19, 20, 21, and 11]. TWI is associated with disease progression and can also be dynamic in 12% of patients [26]. TWI V1-V3 is normally the second most common ECG abnormality in ARVC, behind TAD [19, 20]. In cases where ARVC primarily affects the LV, TWI presents in left precordial leads, V4, V5 and V6 [27].

Management

Management is largely based on preventing SCD caused by VAs and reducing the risk of heart failure (HF). SCD due to VAs can occur at any point in the disease course. HF is primarily caused by myocardial loss and therefore cannot be controlled, but rate-related heart failure due to recurrent VAs can generally be avoided [28]. Due to the wide clinical presentation and varied disease course, management should be individualised to the patient [29].

Current NICE guidelines recommend that ICD’s can be a treatment option for people with familial conditions such as ARVC. Several factors require the consideration of an ICD - these are: involvement of the left ventricle, bi-ventricular dysfunction with clinical signs of HF, previous cardiac arrest, VT with haemodynamic compromise, VF and syncope. The British Heart Rhythm Society recommends an ICD in patients who have ventricular fibrillation, a cardiac arrest or poorly tolerated VT. An ICD should be considered in those with ventricular arrhythmias and severe structural disease. They state that the benefits of an ICD in asymptomatic patients may not outweigh the risks. Of the patients with an ICD inserted 48-78% had an appropriate ICD therapy. Fourteen percent of ARVC patients had an ICD-related complication and 16-33% had inappropriate shocks [30, 31]. VT-stimulated during invasive electrophysiological studies has variable ability at predicting appropriate ICD therapy and therefore has limited practical value [11, 30, 32, 33, 34, 35, and 36].

Anti-arrhythmic drugs that help to control recurrent VAs include amiodarone, sotalol and beta-blockers. An ablation for VAs is of limited use in ARVC due to the progressive nature of the condition. However, in circumstances of symptomatic, drug-resistant VAs, an ablation may help [9].

Patients with ARVC are advised to restrict exercise to “mild” or “moderate” [37]. It has been suggested that exercise increases the mechanical force on the heart and causes the weakened desmosome to breakdown causing the RV enlargement and VAs [38,39]. Due to the genetic link of ARVC, screening should be offered to all first-degree relatives.

References


