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Arrhythmogenic right ventricular cardiomyopathies (ARVC): Diagnostic challenges from imaging to genetics

Short title: ARVC: Diagnostic challenges from imaging to genetics

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary cardiomyopathy, predominantly affecting young males, regardless of ethnicity or race. Due to its variable penetrance, females usually have milder and less malignant phenotypes and it may be diagnosed in older individuals. Accordingly, some affected individuals may remain asymptomatic, while in others sudden cardiac death represents the inaugural symptom. Exercise-related palpitations and syncope are red-flag symptoms in otherwise healthy adolescents and young adults and should be fully investigated, considering ARVC as a potential diagnosis. Clinicians should adopt a cardiomyopathy-oriented mindset which is focused on recognizing suspicious electrocardiogram, structural abnormalities and family history of sudden cardiac death. Complete baseline-investigations should be performed in all individuals

in whom ARVC is suspected, regardless of their symptoms. These include multi-modality imaging (echocardiogram, cardiac magnetic resonance imaging), electrocardiogram monitors and maximal exercise tolerance tests. Genetic testing should be regarded as the final piece of the puzzle and offered in individuals with a high pre-test probability. A clinically actionable result allows for predictive family testing and pre-implantation diagnosis. Importantly, it should be offered only with appropriate pre and post-test counselling. Both clinicians and patients should understand that not identifying a disease-causing variant does not exclude ARVC. Finally, three clinical cases illustrating the potential caveats in diagnosing ARVC are discussed.

Key words: arrhythmogenic right ventricular cardiomyopathy

INTRODUCTION: EVOLVING UNDERSTANDING OF ARVC

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an umbrella-term for a group of genetically determined heart muscle disorders, in which the right ventricular (RV) myocardium is replaced by fibro-fatty infiltrate. This is due primarily to abnormalities of the desmosomal proteins caused by mutations affecting the corresponding genes. In turn, this leads to an impaired myocardial architecture, with ventricular dilatation and systolic impairment, but also to marked electrical instability.

ARVC remains a rare cardiac condition. The prevalence ranges from 1:2500 to 1:5000 individuals, making it far less frequent than other cardiomyopathies, such as hypertrophic cardiomyopathy (1:500) [1, 2]. By contrast, ARVC is frequently reported as the most prevalent cardiomyopathy by registries investigating sudden cardiac death in young individuals [3, 4]. This highlights the condition’s malignant course and dire prognosis, even in otherwise asymptomatic young individuals. The usual age of diagnosis is in adulthood, between the ages of 20 and 40, albeit some asymptomatic individuals may be diagnosed much later in life through family screening, given the variable penetrance of the condition in the same family. ARVC has been traditionally associated with the Caucasian population from the Mediterranean basin. Considering data from multiple dedicated ARVC registries from different countries, the condition does not appear to have a propensity towards a specific race or region [5]. Gender influences the prevalence and prognosis of the condition. Men are more likely to be affected and express a more malignant phenotype, perhaps in the context of sex hormones and higher exercise workload [6].

The original International Task Force Criteria for the clinical diagnosis of ARVC were published in 1994 and included structural, histological, electrocardiogram (ECG), arrhythmic features as well as family history. These criteria were highly specific, as they were based on the more typical forms of this condition, seen in probands or individuals who died suddenly because of ARVC. Hence, they lacked sensitivity for early diagnosis or family screening [7]. Based on the progress made in imaging and cardiogenetics, the 2010 Proposed Modification of the Task Force Criteria included cardiac magnetic resonance imaging [MRI] findings and the identification of pathogenic mutation as a major criterion [7]. In order to incorporate individuals presenting with early phenotypes, two additional diagnostic thresholds were introduced: possible and borderline. Importantly, it is this version of the Task Force Criteria which acknowledged anterior T-wave inversion, defined as inverted T-waves in V1–V3 or beyond in individuals over 14 years of age in the absence of right bundle-branch block, as a major criterion, as they were previously considered only a minor criterion [7]. The 2020 proposed Padua Criteria introduced a paradigm shift in the diagnosis of ARVC, as they acknowledged arrhythmogenic cardiomyopathy as a spectrum which may predominantly affect either the right or left ventricle (LV), or both, while highlighting fibro-fatty myocardial replacement as the common and distinctive feature [8]. Certain genotypes (*DSP*, *PLN*) have a more prominent LV involvement, with little RV involvement, which would not allow for a formal diagnosis to be made according to the 2010 criteria [9, 10]. Hence, the 2020 Padua Criteria aimed to address this gap to benefit the care and surveillance of patients with arrhythmogenic cardiomyopathies, as well as of their families. Furthermore, in a large registry of sudden cardiac deaths due to arrhythmogenic cardiomyopathy, histology confirmed biventricular involvement in 70%, whereas exclusive RV involvement was rare (13%) [11]. The exact frequency of biventricular involvement in clinical practice is difficult to estimate, as histologic examination is not routinely performed. The frequency also depends on the desmosomal mutations identified in the studied population. The likelihood of identifying LV abnormalities depends on the imaging method employed. For instance, LV systolic impairment or dilatation, detectable also by echocardiography, seem to be less frequent than late gadolinium enhancement, detectable only by cardiac MRI [12, 13]. Thus, when cardiac MRI is systematically performed in patients with a suspicion of ARVC, LV involvement is frequently identified. The extent of LV involvement may be variable and disproportionate to the RV involvement.

The current review will focus on the RV involvement, which represents an important and relevant clinical entity, as the 2023 ESC Guidelines for the management of cardiomyopathies

maintain ARVC as a distinct phenotype in the classification of cardiomyopathies [14]. A comprehensive comparison between the 2010 Proposed Modification of the Task Force Criteria and 2024 Proposed Diagnostic Criteria for Arrhythmogenic Cardiomyopathy (European Task Force consensus report) is detailed in Table 1 [7, 15].

Diagnosing ARVC — scenarios and challenges

Symptoms and clinical presentations

Symptoms in individuals with ARVC vary according to the phase of the disease. In the early phases, structural abnormalities are not significant enough to cause right-sided heart failure symptoms and patients would very rarely mention fatigue or exertional dyspnea. Palpitations are commonly reported and they can be more pronounced with exertion. Syncope may also occur. Unheralded or exercise-induced syncope should trigger comprehensive investigations.

Sudden cardiac arrest can be the first symptom, particularly in young individuals. Arrhythmogenic cardiomyopathy with right and/or LV involvement was the most prevalent cardiomyopathy identified in a cohort of adolescents (ages 10–19) who died suddenly [4].

Right-sided heart failure symptoms are usually reported by individuals who already have an established diagnosis of ARVC as RV dilatation and impairment occur in the later phases of the disease. In advanced cases, with severe structural or arrhythmic phenotypes, one should consider referral towards specialized centers who can offer advanced heart failure treatment options, including heart transplant [16]. When the RV remodelling becomes clinically significant, the desmosomal reserve is lost and the functional decline towards an advanced NYHA class can be steep.

Rarely, in patients already implanted with an ICD, heart failure symptoms may be precipitated due to lead-related tricuspid regurgitation. ARVC patients are a challenging population for device implantation because of the extensive and dynamic RV remodeling. Difficult lead placement occurs in 18.4% of patients, while lead malfunction and displacement were reported in 9.8% and 3.3% of patients [17]. Tricuspid regurgitation worsens by at least one grade in 20% of patients after implantation of a cardiac device, but specific data for patients with ARVC are lacking [18].

ECG for diagnosis in ARVC

The electrical abnormalities noted on a 12-lead ECG are very often the earliest changes seen in ARVC. As the ECG changes can be subtle and without associated striking imaging abnormalities, clinicians may be falsely reassured, particularly if the individual is

asymptomatic. Clinicians are particularly aware of anterior T-WI and epsilon waves as red-flags for ARVC. The significance of anterior T-WI in diagnosing ARVC depends on several aspects, such as: the individual's age, the extension and the presence of right-bundle branch block. Negative T waves in leads V1 to V3 or beyond, in individuals who are at least 14 years old, in the absence of right-bundle branch block or ST-segment elevation, are considered a major criterion [15]. Conversely, negative T-waves in V1 and V2 only or beyond V3 in the presence of right-bundle branch block or in children under the age of 14, constitute minor criteria. A challenging situation is often posed by the juvenile pattern in teenagers between the ages of 14 and 16. The juvenile pattern consists of negative T-waves extending to V3 in adolescents <16 years old and is recognized as a benign clinical entity in the absence of other ECG changes, relevant family history or symptoms [19]. Out of an abundance of precaution, a repeat ECG should be sought once the individual is at least 16 years old to ensure the repolarization abnormalities resolved. Importantly, the pattern should not extend beyond V3. Negative T-waves beyond V3 require further investigations even in individuals <16 years old. Epsilon waves are depolarization changes consisting of low-amplitude signals between the end of the QRS and the onset of the T-wave in the anterior leads. They are considered a minor criterion, as they are not entirely sensible, nor specific [15]. They may be seen in other cardiomyopathies, such as cardiac sarcoidosis, and they are subject to great interobserver variability (20), making them unreliable in clinical practice.

Ventricular arrhythmias may be noted on the 12-lead ECG and can raise further concerns in individuals in whom ARVC is suspected. The ventricular ectopic beats with RV origin will have a left bundle-branch block morphology and are considered a major or minor criterion if they are frequent (>500/24 h) and depending on their axis [15]. Premature ventricular contractions with an inferior axis originating from the RV outflow tract (RVOT) are less specific and can be benign, hence only considered a minor criterion, whereas those showing a superior axis (negative in the inferior leads) originate from the RV apex or triangle of dysplasia and would raise further concerns of an underlying cardiomyopathy, hence being considered a major criterion [15].

Hence, suggestive ECG findings, even in asymptomatic individuals with normal baseline echocardiographic studies, should be thoroughly investigated and followed-up with a Holter monitor, exercise tolerance test and cardiac MRI

Imaging for diagnosis in ARVC

Patients undergoing investigations for the suspicion of ARVC should follow a stepwise approach. The transthoracic echocardiogram may be unremarkable in the early stages of the disease, without RV dilatation or impaired systolic function. The 2010 Revised Task Force Criteria considered several RV echocardiographic abnormalities as either major or minor criterion. The presence of a regional wall motion abnormality, except for hypokinesia, which is more subjective and can be easily overdiagnosed, in conjuction with evidence of RV dilatation, documented by measuring the RVOT from two different windows (PLAX and PSAX), or RV systolic function impairment (FAC <33%) were mentioned as criteria for structural alterations [7]. These criteria were not mentioned anymore in the 2020 Proposed Diagnostic Criteria for Arrhythmogenic Cardiomyopathy, which emphasizes the role of cardiac MRI[15]. The limitations of applying the echocardiographic criteria have been acknowledged in certain populations, such as adolescent male athletes or adult endurance athletes, as up to 25% of healthy individuals would meet the major RVOT dimension criterion [21–23]. Perhaps more concerning is that these individuals might also associate ECG changes due to athletic adaptation, such as anterior T-wave inversion, which would potentially result in an erroneous definite diagnosis of ARVC with profound implications. Speckle-tracking has been suggested by several studies as a potential method in further discriminating between physiologic adaptation and pathology in athletes, albeit findings are not entirely consistent, owing to the fact that the extent of RV remodeling is dependent on the sports discipline [24–27], as well as due to the variable quality of RV free wall tracking. Therefore, the limitations of speckle-tracking should be acknowledged and findings should be interpreted with caution in clinical practice. RV dilatation, particularly without functional impairment and obvious regional wall motion abnormalities, should always be further assessed by performing the Qp/Qs ratio, which, if greater than 1.5, indicates a significant left-to-right shunt (Figure 1)

Cardiac MRI is a superior imaging modality in assessing the RV, considering its high spatial and temporal resolution. It is the gold-standard for quantifying ventricular volumes and systolic function. It also enables identifying regional wall motion abnormalities more accurately, as they can be seen and confirmed in two orthogonal planes. Furthermore, flow quantification can be used for estimating the Qp/Qs, valuable in differentiating between ARVC and RV remodeling due to a volume overload. The most attractive feature of cardiac MRI is myocardial tissue characterization through mapping and late gadolinium enhancement. RV enhancement confirmed in two orthogonal views is a minor criterion for structural alteration [15].

ARVC is a desmosomal disease, hence, other cellular junctions would also be affected. This can be seen in patients with Naxos or Caravajal disease, where the cardiac features are

associated with hair and skin abnormalities due to mutations in the *JUP* and *DSP* genes. When it comes to the distribution of junctional proteins, buccal cells behave in the same way as heart cells [28]. Immunofluorescence of the buccal mucosa revealed signal redistribution of certain proteins, such as PKP1 [28]. In a pediatric cohort, no changes in protein distribution were seen until there was clinical evidence of disease. Progressive shifts in the distribution of key proteins correlated with worsening of the disease phenotype, while restoration of junctional signal for Cx43 was seen in patients with a favorable response to anti-arrhythmic therapy [29]. This might be a promising tool in diagnosing and monitoring the disease.

Differential diagnosis of patients investigated for ARVC

"Electrical" phenocopies

The overlap between channelopathies and cardiomyopathies has been further suggested by advances in genomics and proteomics [30]. Notably, loss of expression of desmosomal proteins may also induce sodium channel dysfunction. This is based on experimental studies which have demonstrated molecular crosstalk between desmosomes, voltage gated sodium channels and gap junction proteins found in the intercalated discs [31]. In the early stages of the disease the electrical features, such as resting ECG abnormalities and/or ventricular arrhythmias may be predominant, without evidence of structural remodelling on the cardiac magnetic resonance imaging or echocardiogram. At this stage, the differential diagnosis should include channelopathies, particularly Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Several case reports have shown resting or provokable BrS ECG patterns in patients with ARVC and epsilon-like waves in BrS patients [32–34]. Albeit patients with BrS do not usually exhibit any overt abnormalities on cardiac imaging, histopathologic studies demonstrated an increased collagen content throughout the right and LV myocardium, suggesting an underlying cardiomyopathic process even in patients believed to have a channelopathy [35, 36]. The two conditions may also have a common genetic background, as *SCN5A* variants are associated with ARVC and BrS. Irrespective, ARVC and BrS are two distinct entities, with entirely different clinical evolution, prognosis and risk of sudden cardiac death. Evidence of myocardial fibrosis or RV abnormalities on cardiac imaging in patients with BrS should prompt further investigations and consideration of an arrhythmogenic cardiomyopathy.

CPVT is defined by normal resting ECG and cardiac imaging studies. The electrical hallmark of the conditions is bi-directional ventricular tachycardia (BiVT), which is triggered by exercise or other high adrenergic states. BiVT can also be a feature of ischemia, digoxin

toxicity, myocarditis, Andersen-Tawil syndrome, cardiomyopathies or sarcoidosis [37]. Certain *PKP2* mutations were found to be associated with BiVT. Interestingly, the onset of the electrical manifestations and/or sudden cardiac death in these patients was independent of the structural abnormalities [38]. Genetic testing becomes pivotal in confirming the diagnosis in symptomatic patients (e.g., exercise-induced syncope, sudden cardiac arrest) with bi-directional ventricular arrhythmias and no overt cardiac structural abnormalities. The RYR2 and less often the CASQ2 gene mutations are responsible for CPVT.

In some instances, the suspicion of an underlying ARVC is raised after ventricular arrhythmias are noted on Holter ECG monitor tapes or resting ECG, especially in young patients who mention palpitations or syncope. Differentiating between an idiopathic RVOT VT, which is a benign clinical entity manifesting itself as a paroxysmal monomorphic exercise-induced arrhythmia, and an ARVC-related RVOT VT can be challenging. Electrical features, such as QRS duration, transition or notching, reflect the origin of the RVOT VT, which can be free-wall or septal, but cannot be entirely reliable in discriminating between an idiopathic or cardiomyopathic substrate of the arrhythmia [15]. Apparently benign RVOT premature ventricular contractions have also been noted in desmosomal-gene mutation carriers who did not otherwise show an overt phenotype [39]. An intrisicoid deflection time >80ms and a QS morphology in lead V1, particularly when present in combination, have been suggested as red-flags for an underlying cardiomyopathy [39]. RV regional wall abnormalities (thinning, dyskinesia) can be detected by CMR in idiopathic RVOT, which may correspond to the origin of the arrhythmia [40]. The RV would not be dilated and the systolic function should be normal in this case, as a dilated RV with impaired systolic function would be more suggestive of an underlying cardiomyopathy. The adenosine therapeutical challenge provides further insight, as idiopathic RVOT VT terminates with adenosine. In individuals presenting with VT and no overt structural abnormalities suggestive of ARVC, endocardial voltage mapping can differentiate between an early phase of the condition or idiopathic RVOT VT, by identifying the low voltage areas corresponding to areas of fibro-fatty replacement.

"Imaging" phenocopies

Athletic adaptation is perhaps one of the most clinically significant scenarios in which differentiating between physiology and pathology (ARVC) is crucial for the individual's prognosis and management. It is well known that high-intensity physical activity increases the risk of sudden cardiac death and has deleterious effect on the myocardium in patients diagnosed with ARVC, even in genotype positive/ phenotype negative individuals [41]. Conversely,

physiologic adaptation, particularly in endurance athletes, may raise the suspicion of an underlying ARVC. This is commonly due to evidence of RV enlargement on imaging, or due to suspicious electrical features, such as anterior T-wave inversion (T-WI) or ventricular arrhythmias. When these changes are present, particularly in association, or in a symptomatic athlete (e.g., palpitations or syncope with exercise), comprehensive investigations and follow-up are warranted.

Athletic cardiac remodeling is defined by symmetrical and balanced cardiac enlargement, with the left and RV being proportionally dilated. The specific discipline also affects the degree of remodeling, as athletes involved in mixed and endurance sports would be expected to have larger RV dimensions [42]. There does appear to be a slightly greater increase in RV volumes and as such, a RV/LV end-diastolic volume ratio of 1.2 or less is accepted in athletes [43, 44]. Values greater than 1.2 increase the likelihood of pathological RV dilatation [44]. Physiologic RV remodeling also includes a balanced outflow and inflow dimensions. A disproportionately enlarged RV outflow would be more suggestive of ARVC, rather than athletic adaptation. Lower RV systolic function and lower deformation values are expected in endurance athletes, as the degree of dysfunction seems to be greater the longer the intense exercise is sustained [43].

In extreme cases of endurance training, adverse cardiac remodeling may occur, comprising disproportionate enlargement of the right heart cavities and increased arrhythmogenicity [45]. This has been referred as *exercise-induced ARVC* and the phenotype can be at least partially reversible with detraining [45]. Current thinking suggests an interaction between the genetic make-up of the athlete and the environmental stimulus in the form of high volume and intensity of endurance training. Regional wall-motion abnormalities, such as RV wall aneurysms, should never be considered athletic adaptation. RV late gadolinium enhancement, mentioned as a minor criterion for structural alterations, can be difficult to confirm in CMR studies due to the RV wall being thin, making it an unreliable imaging marker in clinical practice [15]. Insertion point fibrosis is most often limited to the inferior insertion point and should be considered an incidental finding in athletes, if found in isolation [46]. Ultimately, the cardio-pulmonary exercise test may be useful in challenging the athlete's cardiovascular fitness and confirming that it reflects the degree of athletic adaptation.

Anterior T-WI are considered a hallmark of ARVC when seen beyond V2. The ECG abnormalities may be subtle and present before imaging would detect any overt abnormalities. While very rare in the general population, inverted T waves beyond V2 are more common in athletes, particularly in female athletes and elite endurance athletes, explainable in some cases,

at least partially, by the RV apex being displaced towards the axilla [47, 48]. Accordingly, these changes are more commonly noted in individuals with greater ventricular volumes. Generally, when anterior T-WI is due to athletic adaptation, it is limited to V1–V3, but can sometimes extend to V4, preceded by J-point elevation of at least 1mm and seen in isolation [47, 49, 50]. In Afro-Carribean athletes, anterior T-Wi extending to V4 with J-point elevation and convex ST-segment elevation is recognized as a normal repolarization pattern [19]. Preceding ST segment depression or an isoelectric ST segment should increase the suspicion of an underlying cardiomyopathy, albeit in a significant number of white female athletes, the J-point segment may be in line with the onset of the QRS [47]. Another useful marker is the QRS terminal activation delay, which should not exceed 55 ms (Figure 2). Terminal activation delays of at least 55 ms or longer have been associated with larger RV volumes and more impaired RVEF and may represent the sole ECG abnormality in genotype positive individuals who would not otherwise fulfill criteria for diagnosis according to the 2010 Task Force Criteria. In very young athletes, the duration of the terminal activation delay appears to correlate with the years of training, presumably reflecting RV remodelling [53]. The same study found that a terminal activation delay ≥55 ms can be found in isolation in a minority of children (7%) with structurally normal hearts, albeit this was a cross-sectional study without prospective data derived from long-term follow-up [53].

Cardiac sarcoidosis is an infiltrative cardiomyopathy in the context of granulomatous inflammation. RV involvement outside other complications, such as pulmonary hypertension due to pulmonary fibrosis or LV dysfunction, may occur. Ventricular arrhythmias, epsilon waves, RV dilatation, systolic impairment or late gadolinium enhancement are common features. The presence of atrioventricular block is a characteristic of cardiac sarcoidosis. Both conditions may present with or associate flares of myocardial inflammation. Traditionally, positron emission tomography-computed tomography with ^{18}fluorodeoxyglucose (FDG) has been used for cardiac sarcoidosis. Based on the specific FDG uptake pattern, such as multiple noncontiguous perfusion defects with associated FDG uptake or multifocal FDG uptake in combination with extracardiac FDG uptake, specificity can reach up to 100% [54]. Nevertheless, the absence of FDG uptake cannot exclude cardiac sarcoidosis, as in the “burned out” forms, the metabolically active granulomas are replaced by fibrosis. In such instances, the location of late gadolinium enhancement should be carefully interpreted. LV septal or basal subepicardial or RV free wall have been frequently described in cardiac sarcoidosis [54]. For this reason, fusion FDG-PET and CMR imaging should be performed when available. It should not be forgotten that FDG uptake itself reflects an increased metabolism and is not exclusively

specific for cardiac sarcoidosis. As ARVC can present phases of active inflammation, FDG uptake may be occasionally noted [55]. This particular presentation has been described in patients bearing *PKP2*, *DSP* or *DSG2* variants [56]. However, FDG uptake was only exceptionally noted in the RV [55]. Hence, it would be reasonable to consider ARVC as the more likely diagnosis when the there is evidence of significant RV involvement, with minimal or no LV involvement. In cases with active inflammation, it may be difficult to distinguish between ARVC and sarcoidosis. Endomyocadial biopsy should be pursued, as the histopathological features are entirely different (fibro-fatty replacement versus myocardial granulomas). Table 2 summarizes the findings which guide the differential diagnosis between the clinical entities discussed in this section.

Genetics: Utility, implications and limitations

Genetics play an important role in diagnosing individuals with ARVC and their relatives, as the pattern of inheritance is considered autosomal dominant. However, penetrance varies greatly with gender, age and environmental factors, such as exercise. Identification of a pathogenic genetic variant constitutes a major criterion, while a likely-pathogenic variant is a minor criterion [15]. Haploinsuffiency is the mechanism through which loss-of-function mutations become pathogenic. This refers to the fact that having only one functional copy of the gene is not enough to ensure the normal function of the protein encoded by the affected gene. Genes involved in ARVC are classified as desmosomal *(PKP2, DSP, DSC2, JUP*) and non-desmosomal, or genocopies (*TMEM43, PLN, TGFB3, CTNNA3, CDH2, SCN5A*) [15]. Up to 50% of patients with ARVC may be found to harbour at least one disease-causing variant. This means that failing to identify a disease-causing variant does not exclude the diagnosis, as gene-elusive ARVC is an acknowledged clinical entity. Importantly, copy-number variation's analysis should always be performed, since this variant can be found in up to 4% of negative cases [57]. Copy-number variation represents the number of repetitions in the genome of an individual leading to duplications or deletions.

Should a pathogenic or likely-pathogenic variant be identified in an individual (proband or index case), predictive family screening ensues. First-degree relatives can be offered targeted genetic testing for the specific mutation after appropriate genetic counseling. This allows for individuals not harbouring the same genetic variant to be safely discharged and not followed-up, as their risk of developing the condition is similar to that of the general population. Conversely, individuals found to harbour the variant require complete investigations and deep phenotyping to ascertain if they are carriers (genotype positive/phenotype negative) or express

an early phenotype. Regardless, these individuals will require regular follow-up. Importantly, even genotype positive/phenotype negative individuals should be made aware about specific lifestyle recommendations, which include exercise prescription. Pre-implantation genetic diagnosis represents an option for family planning in carriers, if available.

Identification of variant may also have prognostic implications in the proband. It has been acknowledged that the 2019 ARVC Risk Calculator performs better in gene-positive, particularly those with *PKP2* variants, rather than in gene-elusive individuals [58]. In addition, individuals with a DSP or DSG2 variant have an increased risk of developing heart failure compared to *PKP2* carriers [59, 60].

Not exceptionally, in up to 16% of carriers, more than one disease-causing variants may be identified [61]. Compound heterozygosity refers to variants of the same gene being encoded in *trans*, while having mutations in two different genes is called digenic heterozygosity. This has prognostic implications, as the probability of expressing a phenotype or developing malignant ventricular arrhythmias increases (Figure 3) [61].

One of the most challenging results of genetic testing is a variant of uncertain significance, as it is not a clinically actionable result. Variants are classified on a spectrum, which ranges for benign to pathogenic, according to the evidence which supports their ability to cause a particular disease. Variants of uncertain significance are a heterogeneous “buffer” category. Within this category, there are several subcategories (cold, tepid, warm and hot) in which variants may be grouped according to the probability of being likely-pathogenic. This classification is highly dynamic, since new evidence, such as in-silico predictions and updates regarding the prevalence in the healthy population, constantly provides additional insight regarding variants. As such, variants previously considered to have an uncertain significance might be reclassified as likely-pathogenic or, conversely, likely-benign. Discerning between background noise and a potentially actionable result is difficult and requires a multidisciplinary approach, involving cardiologists, clinical geneticist and genetic counsellor. As such, genetic testing should be undertaken by expert centers which have the necessary resources for appropriately interpreting the results and counselling carriers. Variants of uncertain significance should have their significance periodically checked with the laboratory which performed the initial testing. Reclassification might have implications for the individual, but also for the family, as predictive testing is offered for likely-pathogenic or pathogenic variants. Finally, in selected cases, where there is some evidence that the variant may be warm or hot, segregation analysis may be performed. This requires a coordinated effort between cardiologists and clinical geneticists, as relatives being investigated will require deep

phenotyping methods (such as cardiac MRI) to ascertain if they express a subclinical or early phenotype in conjuction with the presence or absence of the genetic mutation. Some limitations of the segregation analysis are related to the variable penetrance of certain genotypes, which is common for desmosomal mutations.

Caveats in diagnosing ARVC through clinical cases

This section illustrates the challenges in interpreting imaging and ECG findings in individuals with suspected ARVC through three different clinical cases. Acknowledging the limitations of each investigation, the value of genetics and serial follow-up is important in preventing misdiagnosis, which would have dramatic prognostic implications.

TAKE-HOME MESSAGES

With the array of available diagnostic tools and evolving knowledge, the diagnostic sensitivity in ARVC has greatly improved. As opposed to the older paradigm, clinicians are more aware of the subtle electrical and imaging abnormalities which may indicate an early phenotype. However, interpretating these findings may be challenging. Hence, diagnosing ARVC has become less straightforward and much more nuanced. When ARVC is suspected in an individual, the clinical context: family screening, presence/absence of symptoms and abnormal ECG and/or imaging findings, guides the sequence of investigations performed for deep-phenotyping and ultimately, risk stratification. Young and/or athletic individuals are particularly challenging populations given the significant overlap between early an early ARVC phenotype, age-related or sports-induced repolarization changes and congenital cardiac disease. Genetic testing further refines diagnosis when used judiciously and has prognostic implications. Furthermore, it may serve as the initial and sometimes sole investigation when employed in cascade family testing with appropriate counseling. Acknowledging the limitations of each investigation and the variable penetrance of ARVC is essential in order to avoid underdiagnosis and in some instances, overdiagnosis. Perhaps the most useful clinical tool available is serial follow-up, particularly for borderline cases, where ARVC cannot be reasonably ruled-out.

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Table 1. Comparison between the 2010 Proposed Modification of the Task Force Criteria and 2024 European Task Force consensus report

Criteria	**2010 Proposed Modification of the Task Force Criteria [7]**	**2024 European Task Force consensus report [15]**	**Comments**
Morpho-functional ventricular abnormalities	Findings were grouped according to imaging method (2D echo/CMR) RV FW RWMA (akinesia, dyskinesia or aneurysm) are	Imaging method is not specifically mentioned MDCT (multidetector computer tomography mentioned)	RV involvement may be segmental, without global dilatation/impairment. Hence, RV FW RWMA have been upgraded to

	a minor criterion only if in association with impaired RVEF or RV dilatation	RV FW RWMA (akinesia, dyskinesia or aneurysm) are considered a minor criterion without impaired RVEF or RV dilatation	a minor criterion on their own
Structural / tissue alterations	Percentage of residual myocites on EMB sample allows for classification into a minor (60%–75%) or major criterion (<60%)	Fibrous replacement of the myocardium in at least one sample is a major criterion, regardless of residual myocites RV LGE on CMR is recognized as a minor criterion	
ECG repolarization abnormalities		Anterior T-wave inversion extending beyond V3 in children <14 years has been added as a minor criterion	Anterior T-WI (V1–V3) with J-point elevation due to early repolarization should be excluded. Extensive T-WI (V1 to V5/ V6) may reflect a more pronounced RV dilatation, rather than LV involvement
ECG repolarization abnormalities	Epsilon waves are considered a major criterion Terminal activation delay and late potential by SAECG are minor criteria	Epsilon waves are only a minor criterion Late potentials are not mentioned anymore Terminal activation duration of QRS (at least 55 ms) remains a minor criterion	ECG filtering and high-interobserver variability were acknowledged as potential issues leading to overdiagnosis of Epsilon waves. Late potentials SAECG were not included as they are not routinely performed anymore and have a low diagnostic accuracy
Arrhythmias		Frequent ventricular extrasystoles (> 500/24 h) with LBBB morphology and non-inferior axis have been upgraded to major criterion History of cardiac arrest due to VF/sustained VT of unknown morphology is acknowledged as a minor criterion	
Family history		No changes	

	ECG						Arrhythmias	Echocardiogram	CMR	LGE
	Anterior TWI	**ST segment**	**Epsilon waves**	**Low QRS voltages**	**AV block**	**RBBB**				
ARVC	+	Isoelectric depressed	+	+	Infrequent	+	PVC, LBBB morphology with superior and/or inferior axis Multiple morphologies NSVT/VT More frequent with exercise	Dilated RV Regional wall motion abnormalities Impaired radiar function Abnormal FW longitudinal strain	Impaired systolic function Increased RVEDV or disproportionate to LVEDV RWMA	+
Sarcoidosis	+	isoelectric depressed	+	+	Frequent High grade AV block	+	PVC, NSVT/VT Multiple morphologies Correlates with location of myocardial fibrosis	Similar to ARVC but with LV involvement	Similar to ARVC but with LV involvement	+ Multifocal LV involvement
Athletetic adaptation	In isolation Can extend to V4	Elevated isoelectric	–	Possible in isolation	First or second degree type 1 If explainable by increased vagal tone (concomitant bradycardia)	+	Usually <500/24 h LBBB with inferior axis Subdue with exercise	Dilated right ventricle Balanced RVOTO/RV inflow dimensions Normal longitudinal function No regional wall motion abnormalities	RVEDV/LVEDV <1.2 Function can be mildly impaired, but increased stroke-volumes No RWMA	RV insertion point Can be seen
Idiopathic RVOT VT	–	–	–	–	–		LBBB with superior axis NSVT/VT Exercise-induced	Normal RV	Normal RV	–

ASD/PFO	+	Isoelectric depressed	-	-	-	+		Dilated RV Normal longitudinal/ radiar function No regional wall motion abnormalities Qp/Qs > 1 or >1.5 if significant	Dilated RV Normal longitudinal/ radiar function No regional wall motion abnormalities Qp/Qs > 1 or >1.5 if significant	-

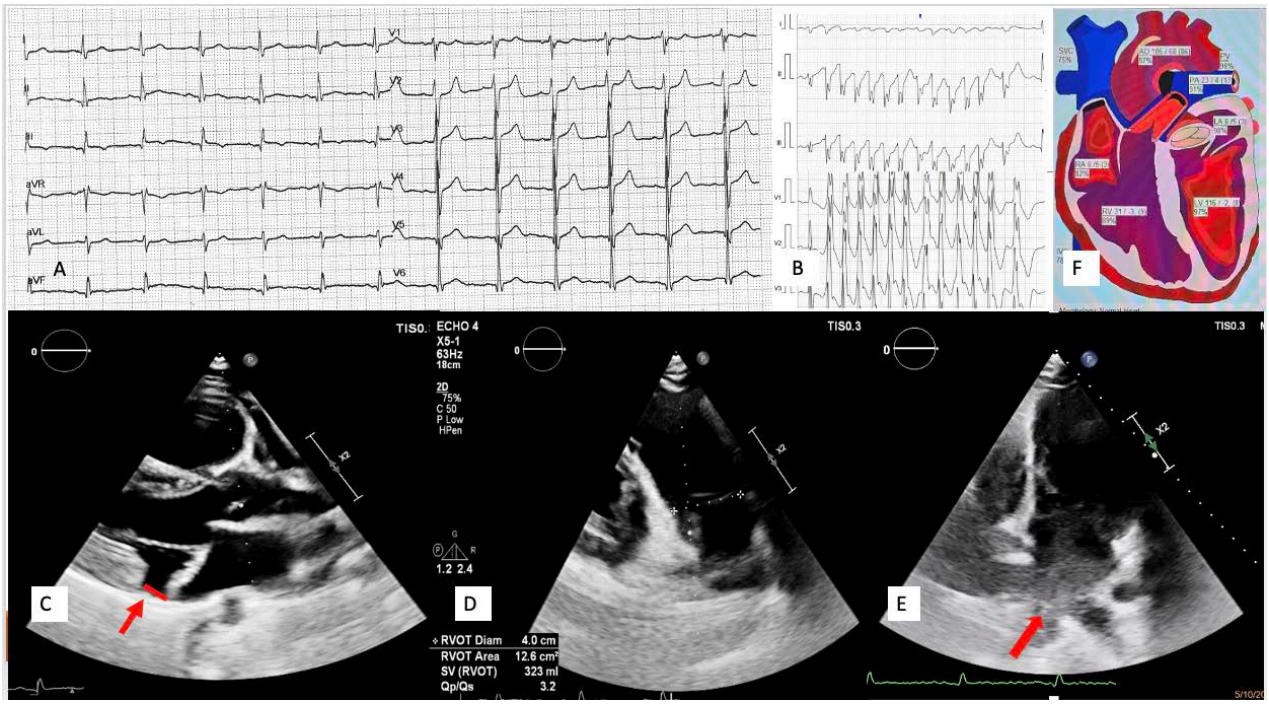

Figure 1. Clinical case 1. 20-year-old male with family history of sudden cardiac death in mother (aged 45) mentioning palpitations, syncope and exertional dyspnea. He is referred with the suspicion of arrhythmogenic right ventricular (RV) cardiomyopathies based on the presence of ventricular arrhythmias and dilated RV, combined with non-sustained ventricular tachycardia and large number of premature ventricular contractions on electrocardiogram (ECG) Holter monitoring. An ICD was implanted for primary prevention prior to his referral. The 12-lead resting ECG (**A**) demonstrates sinus rhythm at 75 bpm, normal PR interval, fragmented QRS in V1–V2 and inverted T-waves in leads III and aVF. The QRS terminal activation duration is more than 55 ms in V2. The 12-lead 24 h Holter ECG monitor (**B**) shows evidence of non-sustained ventricular tachycardia (mean heart rate 190 bpm) with superior axis and right bundle branch block-morphology, suggesting a left-ventricular origin. The transthoracic echocardiogram (**C**) demonstrates mitral annular disjunction (red arrow) and

bileaflet prolapse with mild mitral regurgitation. The RV appears dilated, with a RV outflow tract of 4 cm (**D**) and normal systolic function, without regional wall motion abnormalities. The saline bubble study (**E**) confirms simultaneous contrast in both atria (red arrow). The Qp/Qs was 3.2 (**D**), which was later confirmed by right heart catheterization. This also showed high oxygen saturations in the RV and pulmonary artery (**F**). The transoesophageal echocardiogram and subsequent cardiac computed tomography allowed for the final diagnosis to be made: sinus venosus atrial septal defect with aberrant drainage of the right pulmonary veins in the superior vena cava with associated mitral valve prolapse with annular disjunction. The patient was referred for surgery for correction of the atrial septal defect and aberrant drainage of the pulmonary veins, and 1 month later the RV volumes were normal

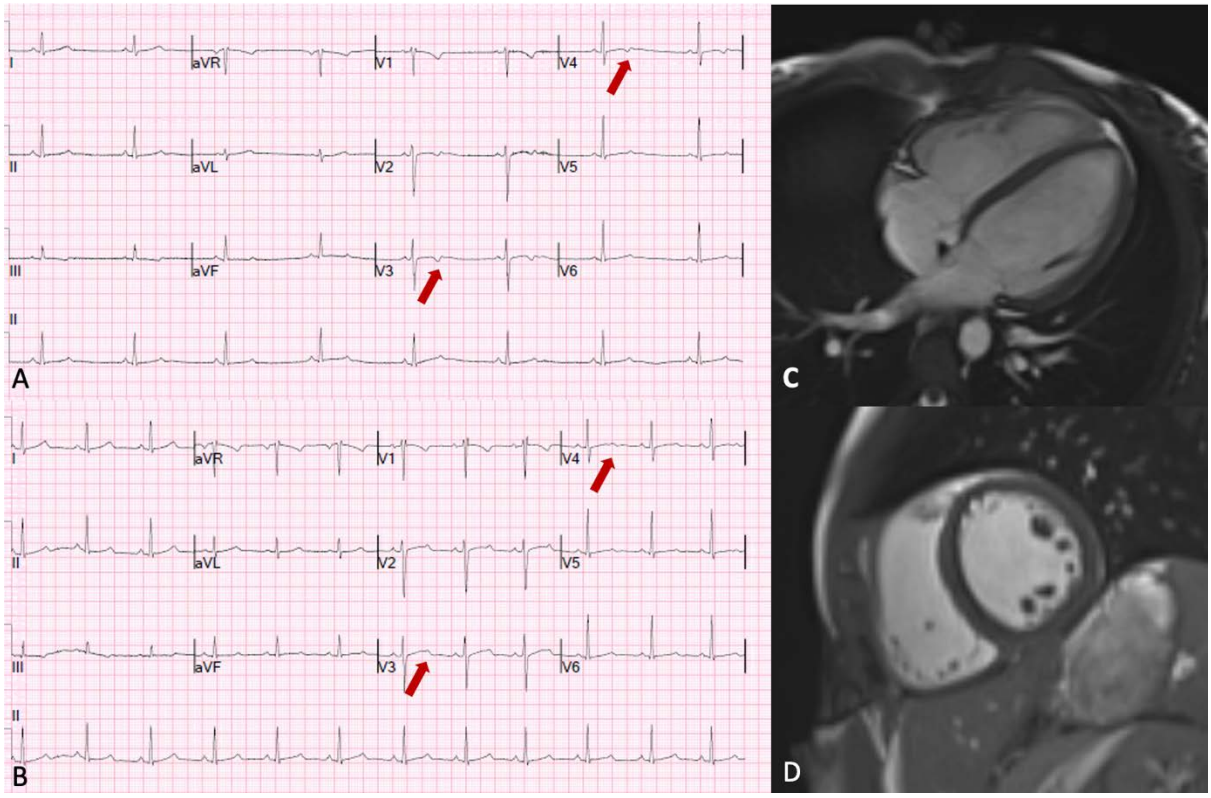

Figure 2. Clinical case 2. 18-year-old Caucasian female, competitive swimmer, asymptomatic and without any relevant family history attends a cardiac screening event. The 12-lead resting electrocardiogram (ECG) (**A**) demonstrates sinus bradycardia at 45 bpm, normal PR interval, rSr' pattern in V1 with a QRS duration of 100 ms and inverted T-waves in V1–V4 with isoelectric ST-segment (red arrows). The QRS terminal activation duration is less than 55 ms in V2–V3. The cardio-pulmonary exercise test confirms a peak VO_2 of 49.2 ml/min/kg (131% of predicted). The exercise ECG tracings are unremarkable, without any ventricular

arrhythmias and the QTc measures 450 ms in the 4th minute of recovery. The cardiac MRI (**C** and **D**) shows mildly dilated ventricles (LVEDVI 108 ml/m^2, RVEDVI 111 ml/m^2) with normal systolic, increased stroke volumes and no evidence of regional wall motion abnormalities or myocardial fibrosis. The second ECG (**B**) performed one year after the first, following 6 months of relative detraining, demonstrates upright T-waves in V2–V4 (red arrows). These investigations allowed to reasonably rule-out ARVC and establish an athlete's heart phenotype

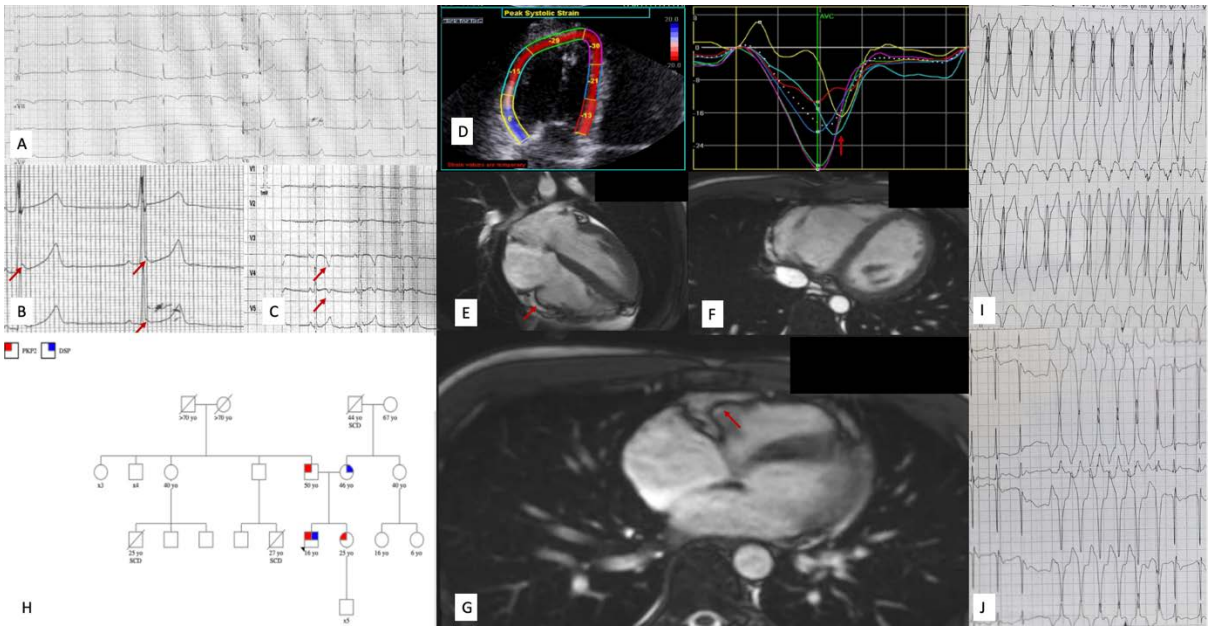

Figure 3. Clinical case 3. 16-year-old asymptomatic Caucasian male, taekwondo player, with a strong family history of premature sudden death, is referred after a screening electrocardiogram (ECG) (**C**) revealed anterior T-wave inversion (V3–V4, red arrows). The current ECG (**A**) demonstrates sinus rhythm at 45 bpm without anterior T-wave inversion, but with evidence of epsilon waves in V3–V4 (**B**, red arrows). Anterior T-wave inversion may show variability on serial ECGs in arrhythmogenic right ventricular cardiomyopathies (ARVC). Importantly, the ECG findings (**B**) should not be mistaken for a juvenile pattern given the patient's age, as T-wave inversion should not extend beyond V3. Speckle-tracking analysis (**D**) confirms reduced right-ventricular (RV) free-wall strain (–17.8%) with abnormal post-systolic shortening on the strain curves (red arrow). The initial 24 h Holter ECG monitor identified 3500 polymorphic ventricular ectopic beats (3%), without non-sustained ventricular tachycardia. The cardiac MRI shows a disproportionately dilated RV (RVEDVi 110ml/m^2) (panels **E** and **F**) with impaired systolic function (RVEF 44%) and dyskinesia of the free-wall (panels **E** and **G**, red arrows). The LV is normal and has preserved systolic function, without

evidence of myocardial fibrosis. The patient fulfils criteria for a definite diagnosis of ARVC. Genetic testing is performed for completion, revealing a likely-pathogenic *PKP2* variant (c.1034+1G>C) and a *DSP* variant of uncertain significance (c.273+5G>A). As there is more evidence suggesting that the variant may in fact be pathogenic according to most in-sillico predictions and publications, it was considered a “hot” variant. Hence, predictive genetic testing ensued in his sister and parents targeting both variants. The *PKP2* variant was identified in his father and sister, while the *DSP* was found in his mother. None of his relatives exhibited a phenotype at the time of family screening. It is well established that penetrance of desmosomal mutations varies greatly among affected family members. In this case, the significant RV involvement at an early age might be explained by the patient’s participation in competitive sports and the existence of two variants identified in different genes. He stopped competitive sports. Three years after the initial diagnosis, the 24 h Holter ECG monitor identified multiple runs of ventricular tachycardia with different morphologies (I and J), with the longest lasting for 30 seconds at an average heart rate of 190 bpm (I). The patient remained asymptomatic, without experiencing syncope. An ICD was implanted in primary prevention