Comparison of Uhl’s anomaly, right ventricular outflow tract ventricular tachycardia (RVOT VT) & arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) with an insight into genetics of ARVD/C

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Among the right ventricular conditions, Uhl's anomaly, arrhythmogenic right ventricular dysplasia / cardiomyopathy (ARVD/C) and right ventricular outflow tract ventricular tachycardia (RVOT VT) are disorders that exhibit pathogenic changes involving the right ventricular (RV) myocardium, and are expected to be severe or milder forms of the same condition. The review focuses on the aspect whether the three RV disorders are a spectrum of the same disease. ARVD/C is the only condition among these to be genetically well characterized. Also, variations in the clinical expression of ARVD/C due to the genetic heterogeneity are examined. Based on clinical manifestations, age at onset, gender ratio and the possible molecular mechanisms implicated, Uhl's anomaly, ARVD/C and RVOT VT may be considered as separate entities. Further, to differentiate between the three RV disorders, the molecular studies on ARVD/C might be helpful. An attempt was made to differentiate between the eleven different types of ARVD/Cs based on clinical symptoms presented including the progression of the disease to the left ventricle, ventricular arrhythmias and clinical characteristics like ECG, SAECG, ECHO and histopathological studies.

Key words ARVD/C - genetic heterogeneity - RVOT VT - Uhl’s anomaly

Introduction

Uhl’s anomaly, arrhythmogenic right ventricular dysplasia / cardiomyopathy (ARVD/C) and right ventricular outflow tract ventricular tachycardia (RVOT VT) involve pathogenic changes in the right ventricular (RV) myocardium. Though complete pathogenic mechanisms have not been discovered for the three disorders, there is a speculation that these may be milder or severe manifestations of the same condition.

In 1952, Uhl described a case in which the wall of the right ventricle was said to be paper thin and almost devoid of muscle fibres, an appearance akin to parchment heart¹. Fontaine et al² described an entity, called arrhythmogenic right ventricular dysplasia, which was characterized, by localized deficiency
or fibrofatty tissue replacement of right ventricular myocardium. Since then, the term ARVD/C has been used increasingly and references to the Uhl’s anomaly have decreased raising the question whether the two conditions are different entities or are variants of a single underlying disorder. Further cases with the morphology of ARVD/C have been inaccurately classified as Uhl’s anomaly. Hence, it became necessary to differentiate between the two conditions.

Right ventricular tachycardia is commonly due to ARVD/C or idiopathic right ventricular ventricular outflow tract (RVOT) tachycardia (VT). ARVD/C is an inherited cardiomyopathy with right ventricular dysfunction due to fibrofatty replacement of myocardium, predisposing to ventricular tachycardia and death. RVOT VT is a benign condition, considered as a primary electrical disorder in the absence of structural heart disease. Frequency of symptoms and history of syncope are similar in ARVD/C and RVOT VT. Detailed analyses using MRI, SAECG and endomyocardial biopsy have detected structural abnormalities in patients with RVOT VT were similar to those seen in the early stages of ARVD/C. Hence, to know whether the two conditions represent separate entities or together form a continuous spectrum of a disease is clinically important for better prognosis and management.

Uhl’s anomaly and RVOT VT, severe and mild forms of ARVD/C?

ARVD/C and Uhl’s anomaly are considered as different manifestations of the same disease. In Uhl’s anomaly, there is virtually complete absence of the myocardium of the parietal wall of the right ventricle and the parietal wall is composed of the opposing endocardial and epicardial ventricular surfaces, with no fatty tissue interposed between these layers. These changes are congenital and diagnosed by foetal echocardiography. ARVD/C is characterized by patchy and localized replacement of the parietal wall of the right ventricle by fibrofatty tissue. This adipose replacement occurs primarily within the ventricular outflow tract, inlet or apical regions, sometimes progressing to the left ventricle. The clinical presentation of Uhl’s anomaly includes cyanosis, dyspnoea and right-sided failure while patients with ARVD/C exhibit ventricular arrhythmias that may range from asymptomatic ventricular complexes to ventricular fibrillation. Uhl’s malformation is usually diagnosed in neonatal or infant life, while ARVD/C patients manifest symptoms during adolescence. In a study, the male: female ratios for Uhl’s anomaly was found to be 1.27:1, while for ARVD/C it was 2.28:1, this difference in the degree of male predominance was considered significant. Uhl’s anomaly has been associated with other disorders like dysplasia of the tricuspid valve, pulmonary atresia and persistent ductus arteriosus, while ARVD/C has been seen as a part of a syndrome with hair and skin abnormalities inherited in an autosomal recessive form or as an isolated condition which is inherited in an autosomal dominant fashion.

James suggested that both conditions share a common pathogenesis of apoptotic dysplasia. In Uhl’s anomaly the apoptotic process may be incessant and starts early in infancy or childhood with complete destruction of RV wall, whereas in ARVD/C there may be episodic apoptosis beginning in adolescence. Though the pathogenic mechanism in ARVD/C is not completely understood, it is believed that defects in desmosomal components, which provide mechanical coupling between the intermediate filaments and the cytoplasmic membranes of adjacent cells, may compromise its adhesive function, predisposing to myocyte detachment and death. Further, as the regenerative capacity of myocardium is limited, fibrofatty substitution is observed as repair mechanism.

Gras et al showed that the suppression of the signaling of canonical Wnt/β-catenin pathway could be the pathogenic mechanism underlying ARVD/C. The probable molecular mechanism hypothesized was that by mutating desmosomal protein impairs desmosomal assembly releasing free plakoglobin from the desmosomes, which could translocate into the nucleus and through competition with β-catenin suppress signaling through the canonical Wnt/β-catenin–Tcf/Lef pathway. Suppression of Wnt/β-catenin signaling provokes adipogenesis, fibrogenesis, and apoptosis, the characteristic hallmark of ARVD/C. The mechanism involved in Uhl’s anomaly would probably involve the factors that would either trigger apoptotic pathways or fail to protect from apoptosis leading to complete loss of right ventricular myocardium. Wnt pathway has not been implicated in Uhl’s anomaly till date but apoptosis can be triggered by many factors including the components of the Wnt pathway.

In the canonical Wnt pathway, frizzled receptors signal to the dishevelled (Dsh) protein, which causes accumulation of cytoplasmic β-catenin. After
translocation to the nucleus, β-catenin activates T cell factor (TCF)-dependent target genes. Human frizzled receptor hFz5 induces apoptosis and the C-terminal region of the cytoplasmic tail of hFz5 shares significant similarity with the corresponding region of Xfz8a (frizzled receptor in Xenopus), required for JNK (a family of stress-activated serine/threonine kinases) activation and apoptosis. Wnt ligand Xwnt5a is a negative regulator of apoptosis induced by Xfz8. A similar process might be expected in Uhl’s anomaly where the Wnt ligands fail to suppress the apoptosis leading to complete loss of RV myocardium. Studies in this regard are required to implicate or rule out this pathway in Uhl’s anomaly.

Mallat et al showed that apoptosis could be the primary process that precedes fibrofatty replacement of myocardial tissue in ARVD/C unlike in Uhl’s anomaly where the only process of apoptosis is reported.

The mechanism operating in ARVD/C should be essentially different from the apoptosis triggered in Uhl’s anomaly as in the later condition there is complete loss of RV myocardium unlike in ARVD/C where it is assumed that apoptosis process not being continued incessantly but being only episodic both spatially and temporally and result in the focal loss of myocardium in a few limited regions or may be more diffused. Further, there is no fibrofatty replacement of myocytes observed in Uhl’s anomaly in contrast, which is the main pathological feature observed in ARVD/C. The difference in clinical expressions and the probable pathogenic mechanisms in these two conditions indicate that Uhl’s anomaly and ARVD/C may be separate entities.

In right ventricular outflow tract (RVOT) ventricular tachycardia (VT), which occurs predominantly in young adults, the origin of VT in RVOT tachycardia is usually in the septum, while for ARVD/C it is in the parietal wall. Kinoshita et al reported mild fibrosis and fatty infiltration in 8 of the 12 patients with RVOT VT. In the 12 lead ECG, the mean QRS duration is longer in ARVD/C patients compared to RVOT VT in all the leads. Late potentials on signal averaged electrocardiogram were not present in RVOT VT patients but were present in 78 per cent of the patients with ARVD/C. Unlike ARVD/C patients, none of the RVOT tachycardia patients had structural abnormalities on echocardiography or angiography, further no major structural abnormalities were observed in RVOT VT patients in MRF. Follow up of patients with RVOT VT has shown that they do not appear to progress to ARVD/C but RVOT VT was reported as a localized form of ARVD/C in 50 per cent of cases investigated.

Table I shows differences in the clinical expressions of the RVOT VT and ARVD/C. These studies indicate that RVOT VT could be a different entity and not a milder form of ARVD/C and that RVOT VT does not progress into ARVD/C during a period of time. But to identify and distinguish between milder form of ARVD/C andRVOT VT is difficult as there is no technique to either establish or rule out these conditions. As the genetic basis of ARVD/C has been established, milder form of ARVD/C can be identified by screening the family members in the familial cases and the sporadic cases can be distinguished by molecular studies.

The molecular pathology of the disorders affecting the right ventricle has not been identified. The basis of

<table>
<thead>
<tr>
<th>Table I. Clinical expressions of the RVOT VT and ARVD/C</th>
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<tbody>
<tr>
<td>Age at onset</td>
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<td>Sex</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Reports of SCD</td>
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<td>12 lead ECG</td>
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<tr>
<td>SAECG</td>
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<tr>
<td>ECHO</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td>Origin of arrhythmia</td>
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<tr>
<td>Mechanism of arrhythmia</td>
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<tr>
<td>BNP levels</td>
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</tbody>
</table>

SCD, sudden cardiac death; ECG, electrocardiogram; SA ECG, signal averaged ECG; ECHO, echocardiography; BNP, brain natriuretic peptide; PVC, polymorphic ventricular complex; SVT, sustained ventricular tachycardiac; NSVT, non sustained VT; VF, ventricular fibrillation.
preferential affection of right ventricle in the setting of the right ventricular disorders is the difference between the right and left ventricular wall thickness and their adaptation to the pressure of the blood flow against which the myocardium has to pump. Therefore, the left ventricle is thick-walled in order to counter the high pressure of the blood flow while the right ventricle also needs to adapt to the wide variations of the preload, i.e. the volume of blood it needs to accommodate, due to which the thin-walled right ventricle is highly distended. Among these three right ventricular disorders, ARVD/C is the only condition genetically well characterized. The molecular studies would aid in recognizing the condition in the early stages and the asymptomatic family members. It would also help in distinguishing the different types of RV disorders.

Genetics:

Eleven autosomal dominant forms of ARVD/C, all exhibiting incomplete penetrance have been identified. Naxos disease, associated with palmoplantar keratosis and wooly hair, has been identified as a recessive condition. Since, the identification of the first locus for ARVD/C in 1994, eight genes have been identified so far. The list of the genes identified for ARVD/Cs and their clinical manifestations is shown in Table II.

Non-desmosomal genes identified:

Transforming growth factor-beta 3 (TGF-β3): Mutations in untranslated 5' and 3' regions of TGF-β3 gene have been identified in the causation of ARVD/C-1. TGF-β3 induces a fibrotic response in various tissues in vivo and modulate expression of genes encoding desmosomal proteins in different cell types. Experiments have shown that incubation of cardiac fibroblasts in presence or absence of exogenous TGFβ3 revealed increased expression of plakoglobin gene and overexpression of TGFβ3, caused by UTR mutations which might affect cell-to-cell junction stability leading to a final outcome as observed in ARVD/C which is caused by mutations in desmosomal genes.

Cardiac ryanodine receptor gene (RyR-2): RyR-2 is the first gene identified for the condition, which is characterized by the presence of peculiar effort-induced ventricular arrhythmias and high penetrance. This unique form of the condition was named ARVD/C-2. Mutations in RyR-2 gene decrease the binding strength between RyR2–FKBP12.6 and increase the open probability of the channels enhancing Ca²⁺ leakage from the sarcoplasmic reticulum. In turn, the increased cytosolic Ca²⁺ concentration would impair excitation-contraction (E-C) coupling giving rise to arrhythmias and induce Ca²⁺ activated apoptosis/necrosis processes, leading to myocardial damages as reported in ARVD/C patients.

Transmembrane protein 43 (TMEM43): TMEM43 is the recently identified gene for ARVD/C-5. Signaling pathways have been implicated in pathogenesis of ARVD/C. For example, plakoglobin, when freed from desmosomal complexes, translocates to the nucleus where it competes and opposes the action of β-catenin and downregulates the canonical Wnt/β-catenin signaling pathway. Suppression of the canonical Wnt/β-catenin signaling upregulates two adipogenic transcription factors, CCAAT-enhancer-binding protein-α (C/EBP-α) and peroxisome proliferator response elements (PPARγ). A genome-wide scan for PPREs identified 1085 potential target genes of PPARγ, including TMEM43. If TMEM43 is a part of an adipogenic pathway regulated by PPARγ, then perhaps dysregulation of this pathway may explain the fibrofatty replacement of the myocardium observed in ARVC patients.47

Desmosomal genes identified:

Desmosomes are major intercellular adhesive junctions found in all epithelial and cardiac tissues. They provide anchorage of the plasma membrane to the cytoskeleton by interacting with intermediate filaments on their cytoplasmic side, thus contributing to tissue integrity. Desmosomes consist of three major protein families- Cadherins (desmogleins and desmocollins), Armadillo (Arm) repeat proteins (plakoglobin and plakophilins) and plakin (desmoplakin).

Desmoplakin: Mutations in the desmoplakin gene have been identified in the causation of ARVD/C-8 and arrhythmogenic left ventricular cardiomyopathy (ALVC). Mutations at the inner dense plaque, particularly affecting the desmin-binding site of desmoplakin may result in ARVD/C with predominantly left ventricular involvement and clinical overlapping with dilated cardiomyopathy, while the mutations affecting the outer dense plaque of desmosome result in ARVD/C with the ordinary described phenotype indicating that mutations in the same gene at different locations might lead to different phenotypes either ARVD/C or ALVC.

A variant of ARVD/C, where the condition is localized to left ventricle (LV), is called arrhythmogenic left ventricular cardiomyopathy (ALVC). The glaring
Table II. Genes involved in different types of ARVD/Cs and their clinical manifestations

<table>
<thead>
<tr>
<th>Gene</th>
<th>TGFβ-3</th>
<th>Desmoplakin</th>
<th>Plakophilin-2</th>
<th>Desmoglein-2</th>
<th>Desmocollin-2</th>
<th>Plakoglobin</th>
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<tbody>
<tr>
<td>Ventricular Arrhythmias</td>
<td>NSVA</td>
<td>SVT, NSVT, PVC and VF</td>
<td>SVT, NSVT, PVC and VF</td>
<td>SVT, NSVT, PVC and VF</td>
<td>NSVT with LBBB morphology</td>
<td>SVT</td>
</tr>
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<td>ECG</td>
<td>- T-wave inversion from V1-V5</td>
<td>- T wave inversion from V1-V5</td>
<td>- Prolongation of QRS</td>
<td>- PQ Prolongation</td>
<td>- Low voltages of QRS</td>
<td>- Complete RBBB</td>
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<td></td>
<td>- Prolongation of QRS in V1, V2 or V3</td>
<td>- T wave inversion from V1-V5</td>
<td>- Low voltages of QRS</td>
<td>- Complete RBBB</td>
<td>- Complete RBBB</td>
<td>- ε waves</td>
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<td></td>
<td>- Incomplete RBBB</td>
<td>- ST elevation</td>
<td>- QT dispersion</td>
<td>- T wave inversion</td>
<td>- ε waves</td>
<td>- ε waves</td>
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<td>- T wave inversion from V1-V5</td>
<td>- Prolongation of QRS</td>
<td>- Low voltages of QRS</td>
<td>- Complete RBBB</td>
<td>- Complete RBBB</td>
<td>- ε waves</td>
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<td>- PQ Prolongation</td>
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<td>- Complete RBBB</td>
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<td>RBBB</td>
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<td>RV and LV</td>
<td>RV and LV</td>
<td>RV and LV</td>
<td>RV and LV</td>
<td>not known</td>
</tr>
<tr>
<td>Structural progression</td>
<td>Only RV, no LV involvement reported</td>
<td>RV and LV, predominantly RV</td>
<td>RV and LV, predominantly LV</td>
<td>RV and LV, predominantly LV</td>
<td>RV and LV, predominantly LV</td>
<td>Biventricular involvement</td>
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<tr>
<td>Family history</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Biopsy/Autopsy</td>
<td>+</td>
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<td>+</td>
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<tr>
<td></td>
<td>Extensive replacement type fibrous and fatty infiltration</td>
<td>Myocardial atrophy with transmural fibrofatty tissue replacement in the walls of both RV and LV</td>
<td>Myocardial atrophy with replacement type fibrosis and mild infiltration</td>
<td>Extensive fibrofatty replacement of RV myocardium</td>
<td>Extensive fibrofatty replacement of RV myocardium</td>
<td>Extensive fibrofatty replacement of RV myocardium</td>
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<td></td>
<td>Surviving myocytes entrapped within fibrous and fatty tissue</td>
<td>Infiltration of RV by fat with presence of surviving strands of cardiomyocytes</td>
<td>Fibrosis and mild infiltration</td>
<td>Surviving myocytes surrounded by fibrosis embedded fatty tissue</td>
<td>Surviving myocytes surrounded by fibrosis embedded fatty tissue</td>
<td>Surviving myocytes surrounded by fibrosis embedded fatty tissue</td>
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<tr>
<td>Diagnostic criteria</td>
<td>Not fulfilled</td>
<td>Not fulfilled</td>
<td>Not fulfilled</td>
<td>Not fulfilled</td>
<td>Not fulfilled</td>
<td>Fulfilled</td>
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departure from ARVD/C is apparent exclusive left sided nature of the disease\(^5\). Suzuki et al\(^5\) reported a 43 year old man, who initially presented with left sided cardiomyopathy with preserved RV contraction, 10 years later developed biventricular progression. Table III gives the clinical findings of ARVD/C and ALVC. The clinical presentations of ALVC are similar to ARVD/C except that the disease is restricted to LV with a normal RV.

**Plakophilin-2 (PKP-2):** Highest number of mutations have been reported in PKP-2 gene causing ARVD/C-9 thus suggesting the plakophilin may be a frequent cause of the disease. Plakophilin-2 is an essential armadillo-repeat protein of the cardiac desmosome. Plakophils together with other desmosomal proteins, assemble to form cell adhesion complexes, which carry out important functions such as mechanically safeguarding cellular and organ architecture, and participating in signal transduction pathways\(^5\).

**Desmoglein-2 (DSG-2):** DSG-2 is expressed in cardiac tissue and is an important component of desmosomal complex. Screening of this gene identified mutations accounting for ARVD/C and as this is the tenth loci for the condition was named ARVD/C-10\(^5\).

Desmosomes consist of 2 desmosomal-specific cadherin family members desmogleins (DSGs) and desmocollins (DSCs). All cadherins have tripartite functional domains - a calcium-inducible, extracellular amino terminal domain, important for homophilic intercellular associations, with 4 domains (EC1 to EC4), followed by an extracellular anchor domain (EA); a single transmembrane domain; and a cytoplasmic domain anchoring the cytoskeleton, an essential process for cell adhesion. So far all the mutations reported in this region have been observed in the highly conserved domains of DSG-2 and it is possible that even a single amino acid change could result in differences in molecular affinity and possibly in the abolition of the adhesive capacity of cadherins.

**Desmocollin-2 (DSC-2):** As desmocollin-2 (DSC-2) is also a component of desmosomal complex, screening of this gene was initiated and mutations were identified causing ARVD/C-11. DSC-2 plays a crucial role in cell adhesion and tissue morphogenesis, it is speculated that absence of DSC-2 or incorporation of mutant DSC-2 in desmosomes would result in structurally and functionally impaired desmosomes. This corroborates with the widely accepted “desmosomal model” hypothesis\(^5\), according to which under conditions of mechanical stress, impaired desmosome function due to desmosomal gene mutations would lead to detachment and death of cardiac myocytes followed by inflammation and fibrofatty replacement\(^7\).

**Plakoglobin:** Earlier mutations in plakoglobin were reported in a variant of ARVC called Naxos disease, which is characterized by signature features of ARVC accompanied by diffuse non-epidermolytic palmoplantar keratoderma (NEPPK) and wooly hair (WH)\(^5\), a recently identified novel autosomal dominant plakoglobin mutation without any cutaneous and hair

<table>
<thead>
<tr>
<th>Table III. Clinical findings of ARVD/C and ALVC</th>
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<tbody>
<tr>
<td><strong>ARVD/C</strong></td>
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<tr>
<td>ECG</td>
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<tr>
<td>- Negative T-waves in precordial leads</td>
</tr>
<tr>
<td>- QRS prolongation in V1, V2 or V3</td>
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<tr>
<td>- Incomplete RBBB</td>
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<tr>
<td>- ST segment elevated</td>
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<tr>
<td>- Low QRS voltages in peripheral leads</td>
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<tr>
<td>- QRS dispersion (&gt; 20 ms)</td>
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<tr>
<td>- Presence of c waves</td>
</tr>
<tr>
<td>SAECG</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>- Mild to severe RV dilation</td>
</tr>
<tr>
<td>- LV involvement with kinetic abnormality both diffuse and localized</td>
</tr>
<tr>
<td>ECHO</td>
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<tr>
<td>Biopsy/Autopsy</td>
</tr>
<tr>
<td>RV dilation with extensive replacement type fibrosis and fatty infiltration</td>
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</table>

ECG, electrocardiography; LBBB, left bundle branch block; VF, ventricular fibrillation; SVT, sustained ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; PVCs, poly ventricular complexes
abnormalities. Plakoglobin is also known to participate in Wnt-signaling pathways, where it is associated with Tcf/Lef transcription factors and regulates functions such as cell proliferation and apoptosis. Different mechanisms leading to altered turnover kinetics of plakoglobin might be responsible for the two variants - Naxos disease with skin and hair abnormalities and dominant ARVC form.

Clinical pathology:

ARVD/C may manifest in the following clinical phases: concealed, overt, right ventricular failure or biventricular failure pump phase. In the early concealed phase, individuals are often asymptomatic but may be at a risk of sudden cardiac death, notably during extreme exertion. Structural changes are absent or subtle and are frequently confined to one region of the triangle of dysplasia: the inflow, outflow, and apical portions of the RV. The second phase marks the onset of the overt electrical disorder, with symptomatic arrhythmia of RV origin and more prominent RV morphological abnormalities readily discernible by conventional imaging. In the third phase, diffuse RV disease results in an isolated right heart failure. LV involvement with biventricular pump failure occur in the final stage, leading to a phenotype that may resemble dilated cardiomyopathy.

Initial symptoms:

The first clinical presentation could be sustained ventricular tachycardia, palpitation, syncope, chest pain, recurrent ventricular tachycardia or cardiac arrest due to ventricular fibrillation. Clinically ARVD/C is responsible for approximately 5 per cent of unexplained sudden cardiac death (SCD) cases in young athletes in United States and 27 per cent of such cases in Italy. Cardiac deaths in ARVD/C are accounted by sudden death and heart failure. Hulot et al. reported heart failure as the cause of death in about two-thirds of the patients investigated.

Angiotensin converting enzyme (ACE) polymorphism was analyzed in ARVD/C patients and a high prevalence of DD genotype in patients with syncope was observed and might be useful in identifying high-risk patients for syncope.

The clinical manifestations of the probands harbouring plakophilin-2 genes mutations are similar to patients with other ARVCS except that probands with DSP mutations are characterized by a high occurrence of sudden death even in the concealed phase, while individuals harbouring plakophilin-2 genes mutations express the disease earlier in life, as determined by age at first clinical manifestation and age at first arrhythmias.

Structural progression of the condition:

Biventricular involvement is expected as the disease progresses. Involvement of the RV or LV is dependant on the site of the mutation in patients carrying desmoplakin gene mutation. Mutations in the plakophilin-2 genes cause the disease affecting predominantly the RV, while desmocollin-2 gene mutations may be more frequently associated with left ventricular phenotype without significant right ventricular involvement. LV involvement is not observed in patients with TGF β-3 gene mutation.

Diagnosis:

A Task Force of the European Society of Cardiology has proposed the criteria for the clinical diagnosis of ARVD/C categorized as the major and minor criteria, based on the identification of structural abnormalities, fatty or fibrofatty replacement of RV myocardium, electrocardiographic changes, arrhythmias of RV origin, and familial disease. The diagnosis is fulfilled in the presence of two major criteria or one major plus two minor criteria or four minor from different groups. Not all patients' family members fulfilled diagnostic criteria.

A modified diagnostic criteria has been proposed to screen and identify the family members of the probands, who were either asymptomatic or exhibited mild symptoms.

ECG: The ECG in ARVD/C patients usually show a regular sinus rhythm, with a QRS duration of greater than 110 milliseconds in lead V1 and an inversion of T waves in precordial leads V1-V3. The extent of T wave inversion in the precordial leads beyond lead V1 correlates with the extent of right ventricular involvement. Prolongation of QRS duration in the right precordial leads reflects late conduction in right ventricle. Small electrical potentials occurring at the end or immediately after the QRS complex in leads V1 or V2, called δ (epsilon) waves are present in approximately 30 per cent of ARVD/C patients who have VT. δ waves reflect delayed depolarization in the right ventricle.

All the patients showed repolarization abnormalities in 12 lead ECG and a T wave inversion in the leads V1 through V2, V3, V4 or V5 with complete or incomplete right bundle branch block (RBBB). Epsilon waves
were observed in the probands carrying the mutation in the genes coding for the desmosomal proteins but not in the patients with TGFβ-3 gene mutation.

**Signal averaged ECG (SAECG):** Signal-averaged ECG has shown a significant correlation between presence of late potentials and occurrence of sustained VT. Ventricular late potentials appear to arise from the areas of structurally abnormal myocardium in which ventricular activation is delayed and asynchronous. Delayed fragmented electrical activity is probably related to re-entry of ventricular arrhythmias. Late potentials in SAECG are observed in all the probands irrespective of the type of ARVD/C.

**Ventricular arrhythmias:** The peculiar histopathology of the disease predisposes the patient to malignant ventricular arrhythmias. VT is generally believed to be re-entrant and is usually accompanied by abnormalities of ventricular activation. The presence of zones of altered myocardium, characterized by fibrofatty infiltration, can create re-entry circuits representing the substrate for repetitive ventricular arrhythmias. Ventricular tachycardia (VT) and ventricular fibrillation (VF) are documented causes of sudden death in ARVD/C.

In all the ARVD/C patients irrespective of the type, left bundle branch block (LBBB) type VT is documented (either sustained or non sustained or both). Probands with TGFβ-3 gene mutation presented only non sustained ventricular tachycardia/ arrhythmias while probands carrying the mutation in the either desmoplakin or plakophilin-2 genes presented with all the four types – sustained ventricular tachycardia, non sustained VT (NVST), polymorphic ventricular complexes (PVCs) and ventricular fibrillation.

**Echocardiographic studies:**

Moderate to severe dilation of RV with RV wall motion abnormalities are observed in all ARVD/C patients. LV involvement with LV kinetic abnormalities of diffuse and localized forms were observed in all the probands except in the patients with TGFβ-3 gene mutation, in whom there was no LV involvement.

**Familial studies:**

All ARVD/C patients carrying mutations in different genes (TGFβ-3, DSP, PKP-2, DSG 2 and DSC-2) had positive family history. Not all family members of the probands fulfilled the diagnostic criteria but fulfilled the modified diagnostic criteria though they carried the mutation.

**Histopathological findings (autopsy/biopsy):**

RV dilation was observed along with extensive replacement type fibrosis and fatty infiltration. Surviving myocytes entrapped within fibrous and fatty tissue showed degenerative changes and abnormal nuclei. ARVD/C is one of the major causes of sudden death and has variable penetrance and expressivity. Although genotypically family members of the patient carry the mutant allele, phenotypically they might be asymptomatic. As the disease progresses, they might get symptomatic or may manifest sudden death. Hence genetic testing would aid in identifying the mutation carriers and help in treatment and prognosis.

**Conclusions**

Based on the symptoms, clinical investigations and the probable molecular mechanisms implicated, the three conditions, viz., Uhl’s anomaly, ARVD/C and RVOT VT may be considered as separate clinical entities. Different ARVD/C types can be differentiated to an extent based on the clinical symptoms.

Mutations in the two non desmosomal genes, cardiac RYR-2 and TGF β-3 implicated in ARVD/C-2 and ARVD/C-1 exhibit different clinical presentations which are easily distinguishable from the symptoms and clinical manifestations exhibited by the desmosomal gene mutations. But in a study, two patients harbouring the same mutation in PKP-2 gene (almost same age, the only difference is the gender of the patients, unpublished data) exhibited different clinical phenotypes further complicating the condition to understand and differentiate. Can gender be another parameter that could affect the severity of the condition, has to be considered. The reports on monozygotic twins suggest the role of environmental factors on the expression of the disease. The identification of different types of ARVD/Cs based on specific symptoms would aid in genotype-phenotype correlations.

**References**


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