Arrhythmogenic Right Ventricular Cardiomyopathies and Sudden Death

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Historical background:

Arrhythmogenic Right Ventricular Dysplasia (ARVD) was the denomination originally proposed in 1977, in a book chapter reporting the results of anti-arrhythmic surgery for the treatment of ventricular tachycardia (1). This original description is reproduced in annex I. Identification of ARVD as a "Cardiomyopathy" was originally made by the same group, in the early 80s, in a paper accepted for publication in the American journal "Cardiology", but it was never published (annex II). The term "ARVC" was finally introduced in 1988 (2). Pr. Fulvio Camerini later supported this term during the preparation of the First International Symposium on ARVD held in Paris in 1996. It was considered by him appropriate to incorporate other diseases, known under a different name, or new diseases that would be discovered because of foreseen advances in genetics and molecular biology. Catecholaminergic VT and Desmoplakin related RV diseases are examples demonstrating that his prediction was correct. Therefore, the term RV Cardiomyopathies (plural) appropriately encompasses all the clinical forms in which ARVD, as described by Marcus et al. in 1982, remains the most frequent form of presentation (3).

The term dysplasia is appropriate since "dysplasia" has been defined as a "trouble in development" (4). A striking example is Uhl's anomaly, first reported at Johns Hopkins Hospital, with localised total absence of RV myocardium (5). The pathology of a typical embryo (27 weeks) with right ventricular aneurysm and adipocytes as well as minor fibrosis, strongly suggested that the disease might start in the embryo (6) (Fig.1).

However, clinical evidence and histology shows that in ARVD, signs of inflammation and/or major fibrosis are due to myocarditis, which look superimposed on the genetic background of (A)RVD (7-9).

Following is our latest proposed classification, based on our clinical experience of more than 300 patients, those provided by the "International ARVD Family Network Group" (ARVD-ARVC-Info.com), as well as our worldwide histological collection of 92 histological cases from antiarrhythmic surgery, autopsy, endocardial biopsy and heart transplant. It also includes the most recent data obtained by genetics and molecular biology, when available.
Since the discovery of the first gene explaining Naxos disease, which is a rare but dramatic form of ARVD (Fig.2) related to a cell-cell adhesion protein, (Fig.3) it was possible to think that all the other proteins of the same structure (desmosomes) (Fig.4), already suspected in ARVD (Fig.5) can be considered as candidate genes involved in the other forms of right ventricular cardiomyopathies. Subsequently an increasing number of genes have been identified. Therefore, right ventricular cardiomyopathies are forming a consistent group of diseases mostly related to anomalies of desmosomal proteins, which can be called "desmosomal cardiomyopathies" within the group of Right Ventricular Cardiomyopathies.

Classification of Right Ventricular Cardiomyopathies

- ARVD:
  Phenotype: This disease is, as is with most of the other forms of ARVC, an inherited condition transmitted in a dominant form with variable expressions and penetrance in family members (20 to 50%). It is generally discovered during adolescence by signs of ventricular arrhythmias originating in the right ventricle (3). **Sudden death** can be the first presenting symptom especially during endurance and competitive sports. It is generally a progressive condition, but the disease may remain stable for decades.

  Histology: The epicardial and frequently mediomural layers of RV myocardium are occupied by fat and fibrosis (Fig.6). Some aspects suggest that the pathologic process starts in the mediomural layers mostly extending toward the epicardium, which can be totally made of fat and fibrosis, wrongly suggesting that the disease progresses from epicardium to endocardium. Fibrosis generally borders or embeds surviving fibers. Full thickness of the RV myocardium is necessary to depict the typical topographic features of the lesions (Fig.6). Therefore, histology is the gold standard to ascertain the diagnosis. The frust forms and forms observed at the beginning of the disease, especially those observed in family members, can be difficult to diagnose.
  Involvement of the left ventricle is frequently observed mostly at the apex, which looks covered by fat. However, some focal zones of fibrosis and fatty tissue can be found all over the full thickness of LV myocardium (10). This may explain the decrease in the LV function found even in the moderate forms of the disease.

  Genotype: Genes identified are coding for Desmoplakin (11) and recently Plakophilin 2 (12) and Desmoglein 2 (13). These genes are parts of the desmosomal structure and fascia adherens, which plays a major role in longitudinal cell-cell adhesion (Fig. 4). However, Transforming Growth Factor (TGF Beta3) is a new gene related to the phenotypic presentation of one of these cardiomyopathies (13). Plakophillin 2 appears currently as the most frequently observed gene (11 to 43% of the series, as well as in our own experience).

- Biventricular Dysplasia:
  Phenotype: Because of the loss of myocardial tissue of the left ventricle, this form frequently leads to congestive heart failure (15).
  Histology: In this form, the same evidence of fatty tissue and fibrosis is observed in both ventricles. However, the disease seems to progress from epicardium to endocardium as opposed to classical ARVD, where fibrosis and fat seems to start in the mediomural layers (16).

- RVD Without Arrhythmia:

  - Quiescent:
    Phenotype: There are no obvious arrhythmias as opposed to the previous form. This might be related to the fact that the arrhythmogenic substrate is totally silent or that minor arrhythmias are present, but not severe enough to lead to hospitalization.
    Histology: In this form, observed in 3.7% of the general population (Fig.7), the typical histologic pattern of ARVD is observed in the RV free wall (17). However, the arrhythmogenic substrate is dormant. It is our understanding that the occurrence of arrhythmias that may lead to **sudden death** is either due to the development of

critical electrophysiologic parameters leading to sustained re-entry or the result of neutrophiles activation or both.

➢ RVD with Congestive Heart Failure:
Phenotype: This can be the result of two different mechanisms. The first is due to major progression of the dysplastic phenomenon, producing more and more myocardium by fat and fibrosis in the right ventricle, and leading to subsequent involvement of the left ventricle by the same disease process. The second is due to a superimposed myocarditis (see below). Because of absence or minor arrhythmias, these cases can mimic Idiopathic dilated cardiomyopathy (18).

❖ ARVD + Superimposed Myocarditis:
Clinical as well as histologic data, may exhibit various forms of myocarditis superimposed on ARVD suggesting a particular susceptibility of dysplastic myocardium to inflammatory phenomena in particular viruses (this concept can be extended to other forms of cardiomyopathies). The presence of coxsackies as well as adenoviruses has been observed in the myocardium of ARVD patients (19, 20). In most cases myocarditis involves both the right and left ventricle. Both the severity of left ventricular involvement and speed of myocarditis progression, determines the prognosis (21). Clinical patterns are quite variable.

➢ Quiescent :
➢ *Phenotype* : Asymptomatic.
➢ *Histology* : presence of lymphocytes is common (0.1-5.5%) in the general population (22). In our opinion it seems nevertheless more frequent in ARVD patients.

➢ Hyper Acute:
➢ *Phenotype:* Fever, asthenia, dyspnea, hypotension, fulminant heart failure and death within a few days (23).
➢ *Histology:* Diffuse round cells infiltration, polymorphonuclear, eosinophils.

➢ Acute:
➢ *Phenotype:* Fever, Chest pain, AV conduction disorder. May last from a few days up to several weeks and is associated with the release of cardiac enzymes (troponine).
➢ *Histology:* Round cells (lymphocytes). Value of endocardial biopsies that may lead to therapeutic implications (Beta-interferon).

➢ Chronic:
➢ *Phenotype:* Moderate clinical signs of heart failure, asthenia, dyspnea, etc.
➢ *Histology:* Healed myocarditis leaves patchy areas of “replacement” fibrosis. Lymphocytes have disappeared or remain in small quantities.

➢ Chronic-active:
➢ *Phenotype:* Moderate clinical signs of heart failure, asthenia, dyspnea, increasing with time, palpitations, syncope, etc.
➢ *Histology:* Myocarditis, which is frequently multifocal, progresses replacing more and more myocardium by fibrosis and patchy zones of adipocytes. Lymphocytes are present.

These multiple forms explain the polymorphism of clinical presentations. We think that superimposed myocarditis is a major cause of the trigger of arrhythmias and **sudden death**. Therefore the pathology of the hearts of patients who died suddenly have shown more frequently than in the common forms of RVD the evidence of signs of inflammation.

Gene mutations explaining viral susceptibility is an open question (Christine Seidman pers. com. CARDIOSTIM 2005).

- Naxos Disease:
  This is a very rare disease discovered in the island of Naxos (Greece) in 24 patients from 6 families (Fig.2). The form of transmission is recessive; some other isolated cases have been discovered in the world.
  Phenotype: The phenotype is identical to classical ARVD associated with Woolly hair and Keratoderma (25). *Histology*: Typical ARVD association. The association of signs of myocarditis and arrhythmias is frequent, as is **sudden death.**
  Genotype: Plakoglobin truncation is the monogenic factor producing the disease (25) (Fig.3). All patients are homozygous. The asymptomatic heterozygous patients may have Right Ventricular Outflow Tract ventricular tachycardia.

- Israelian Desmoplakin Recessive Dysplasia:
  Phenotype: There is a syndrome found in the non-Jewish population of Israel associated with woolly hair, keratoderma and RVD similar to Naxos disease.
  Genotype: Desmoplakin truncation is the monogenic factor producing the disease (26).

- Venetian Desmoplakin Dominant Dysplasia: Transmission is autosomal dominant.
  Phenotype: Seems similar to ARVD.
  Histology: Similar to ARVD.
  Genotype: Desmoplakine located in series between plakoglobin and desmin, supporting the complex actin-myosin, is responsible for the disease (27) (Fig.3).

- Uhl's Anomaly: A rare anomaly.
  Phenotype: Two forms.
  Pediatric form: Newborns (differential diagnosis with Ebstein disease) with congestive heart failure (5).
  Adult form: Arrhythmias, congestive heart failure or both (28). This form is frequently confused with ARVD (29).
  Histology: The pathologic examination is pathognomonic and unmistakable. There is total absence of myocardium on the RV free wall consisting only of epicardium and endocardium separated by a thin layer of adipocytes occupied by coronary vessels, which could exhibit abnormal proliferation of the media. Thus, the wall is, properly speaking, transparent (Fig.8).

- ARVD Mimicking Uhl's Anomaly:
  Phenotype: One personal unpublished case with huge RV. Extremely thin RV free wall mimicking Uhl's anomaly (all imaging techniques).
  Histology: After heart transplant for terminal heart failure, a thin layer of myocardium was present. The wall was translucent but not transparent. This is therefore different from typical Uhl's anomaly.

- Biventricular Spongy Dysplasia:
  Phenotype: Slowly progressing congestive heart failure. One personal case from Portugal (30). No other case in the literature.
- *Histology*: Total disappearance of myocardium in RV with thick endocardium and epicardium. LV dissociated by interstitial fat with minor fibrosis, suggesting apoptosis (29).

- Catecholaminergic VTs:
  Phenotype: Episodes of Polymorphic VTs triggered by effort or psychological stress. High risk of **sudden death**.
  Histology: Two presentations:
  - With structural heart disease: Histology similar to classical ARVD (31).
  - Without structural heart disease: (32).

Genotype: Mutation of the gene coding for RyR2 Ryanodine receptor on Sarcoplasmic reticulum playing a role in the regulation of intracellular calcium (33). The overload of calcium can explain the particular morphology of ventricular arrhythmias. This is different from ARVD arrhythmias, which are mostly the result of slow intramyocardial conduction and reentry.

- Brugada Syndrome (BS) (some patients only):
  Phenotype: Nocturnal **sudden death**, dizziness, "vasovagal syncope". In some cases this syndrome shows an overlapping pattern with ARVD (Fig.9). Nevertheless, effectiveness of Isoprenaline in the BS is in sharp contrast with ARVD, where it is used to induce ventricular arrhythmias. Therefore, it seems appropriate to include in the database only those BS ECG patients who meet the new ARVD criteria (34).
  Histology: Pathology of some cases of BS who died suddenly showed, in 38% of them, structural heart disease, some with signs of inflammation/fibrosis andothers with a typical histologic pattern of ARVD (35).
  Genotype: Multiple mutations in SCN5A that now appears as a cofactor rather than the unique cause of the disease (36).

  Note: The same ECG pattern associated with structural anomalies suggesting ARVD has been described by Nava, Martini and Thiene in the Giornale Ital Cardiol in 1988.

The following subgroup consists of very common arrhythmias, which can be highly symptomatic. With time, a progression can be observed in some patients from isolated extrasystoles to couplets, triplets, short runs of non-sustained VT, sustained VT, incessant VT and ventricular fibrillation, which may specifically lead to **sudden death**.

- Right Ventricular Outflow Tract (RVOT) (about 50% of patients):
  Phenotype: Extrasystoles, runs of repetitive short runs of ventricular tachycardia. Imaging techniques have identified a structural heart disease.
  Histology: A typical pattern of dysplasia localized to the infundibular area has been reported (including small vessels disease [30]) (Fig.10).

- Septal Ventricular Outflow Tract (SVOT): Ventricular extrasystoles progressing to VT have been observed in intraseptal exploration by using a special needle probe inserted inside the RV septum during surgery and showing highly fragmented potentials (Fig.10).

- Left Ventricular Outflow Tract (LVOT): Extrasystoles and VTs have been recently identified. Structural heart disease has not been reported yet.

- Fat Dissociation Syndrome (FDS):
  Phenotype: No symptoms, presence of hypersignal of fat at MRI examination (false positive diagnosis for ARVD). The risk of **sudden death** is very low.
  Histology: Presence of fatty tissue in the right ventricular myocardium has been known by pathologists for a long time. However, its quantitative assessment is recent (Fig.7). In addition, fat in the RV appears to be specific to the human species. This is observed in up to 60% of the general population (37). It has not been observed in the RV of eight non-Bonobo monkeys (17). Therefore, FDS seems to be the result of a mutation that has occurred specifically in the human species. Basically, there is no fibrosis in FDS, which seems less dangerous than ARVD (38). However, our personal experience with several patients recently confirmed by a superb study from Boston has clearly demonstrated that fat in the RV (without fibrosis) is a cause of unexpected death in the postoperative period after heart transplantation (39) (Fig.11). Heart donors with the asymptomatic severe form of ARVD will obviously meet with the same catastrophe.

Borderline Syndromes:

- ➢ Mitral Valve Prolapse: More frequent in cases with predominant fatty transformation close to FDS (40).
- ➢ Carvajal-Huerta disease: Recessive form of transmission, syndromic, mostly affecting the left ventricle with left ventricular involvement by fibrosis without fatty transformation (41).
- ➢ Desmoplakin ALVC is controversial (42).

Differential Diagnosis:

- ➢ RVOT VT with no structural heart disease (43),.
- ➢ Catecholaminergic VT with no structural heart disease (44).
- ➢ Brugada Syndrome (some patients).
- ➢ Pure Myocarditis: This entity produces fibrosis associated with clusters of fat, which can mimic ARVD except that the transmural pattern is absent.
- ➢ IDCM with RV VT and preserved LV function:
- ➢ Heart Sarcoidosis: Can mimic ARVD, however the association of the two diseases has been observed (Fig.12).

Animal Models: ARVD patterns have been observed both in common cats (45) and Boxer dogs (46).

Discussion:

Since the discovery of Plakoglobin explaining the cardiac as well as the cutaneous signs of Naxos disease, the other molecules involved in the cell-cell adhesion proteins, fascia adherens and desmosomes have provided clinical patterns with variations. For example, Naxos disease that has a recessive form of transmission is more severe than the forms of these cardiomyopathies with a dominant form of transmission. However, in a not yet published work presented at AHA 2005, the Johns Hopkins group reported in the “young investigator award” that patients with involvement of plakophillin 2 have earlier and more severe ventricular arrhythmias as opposed to the other patients who tested negative for this protein. This is the reason why we have preferred to isolate the different forms of desmoplakin involvement rather than to include them in the same category. It is however, possible to go one step further. We know that in the same molecule several genes can be involved. This may lead to a further refinement in phenotype classification not yet identified in ARVCs.

In addition to the abnormalities in the mechanical structure of adhesion proteins, molecular biology has also provided new hints to understand distortion of electrical transmission properties. C. Guiraudon et al., was the first to report in 1989 abnormalities desmosomes in ARVD (47),(Fig.5). This observation, which was also confirmed by Roncali et al. in the same journal, leads one of us (GF) to suspect subsequent abnormalities of gap junctions that can be the background of electrical cell-cell conduction anomalies. It was possible with the contribution of Dr Jeff Saffitz from St Louis (Missouri) to demonstrate by immunohistochemistry and confocal microscopy the underexpression of protein Cx43 in the left but mostly the right ventricle of patients with Naxos disease (48) (Fig.13). Therefore, in addition to abnormal gross histological disorganization of RV myocardium it was possible to demonstrate a second factor that can lead to impaired conduction properties, unidirectional block and reentry leading to ventricular arrhythmias, and possibly **sudden death**.

Independently of the structural role played by cell-cell junction proteins they pertain to the armadillo family. It is known that these molecules play a determinant role in the signalling pathway in embryogenesis. A recent work from the Baylor’s College of Houston (49) has reported experiments giving credit to the role of WNT proteins to explain adipogenesis by a genetic phenomenon. These proteins act as a switch. If they are present they inhibit the transformation of precursor cells in adipocytes and favor the development of cardiomyocytes. If the WNT switch is off, cardiomyocytes are inhibited by the development of adipocytes (50). We have observed (unpublished data) that desmosomal betacatenins are translocated to the

nuclear membrane where they can interact on the WNT suppressing the brake, which inhibits adipogenesis and permits the development of cardiomyocytes. This can explain adipogenesis in ARVCs.

Advances in the understanding of the molecular biology of these cardiomyopathies has opened new avenues that may contribute to the treatment of some patients, such as the blocking of adipogenesis in the fetus of a family at risk as identified by advanced techniques of cardiac electric field processing (Fig.14), and thus preventing the risk of **sudden death**.

Risk Stratification in ARVCs:

It is important to realize first that evaluation of risk of **sudden death** and subsequent medical attitude has medico-legal implications. This may explain why in the USA more than in other countries, patients and family members are more frequently considered for ICD implantation as soon as the diagnosis is established or even suspected,.

However the stratification of risk is highly variable depending on the correct classification of each case in its category, as noted above. The clinical presentation is nevertheless the first element leading to the medical attitude. It is presented below with decreasing risk of **sudden death**.

Patients hospitalized for major cardiac arrhythmias:

History of syncope: So-called “Vasovagal syncope” frequently observed in the Brugada syndrome. Evidence of VT, whatever its form, going from nonsustained monomorphic VT to multiple episodes of poorly tolerated VT.

Frequent PVCs. Evidence of couplets, triplets, non-sustained VT, sustained VT.

Frequent and polymorphic PVCs increasing during exercise or psychological stress. This may lead to fast sustained VT and finally VF.

Exercise stress test with increased occurrence of PVCs and VT episodes.

EP study is important to confirm VT and not supraventricular tachycardia with bundle branch block, which is not rare in this condition.

EP study may help to classify the possible risk of **sudden death** if the ventricular arrhythmias are easily induced and are severe, fast VT or VF.

New EP study is also important in severe cases after ablation or drug treatment to confirm that VT is no longer inducible and that the risk of **sudden death** is significantly decreased.

Even if all the exams are within normal limits a possible risk is still there and prophylactic ICD implantation can be considered after patient is informed in the presence of a family member (witness).

In critical cases such as competitive sports persons the recommendations have to be established by a college of experts. Signed document rejecting medical recommendations is important for the physician.

Symptomatically affected family member:

Has to be evaluated with non-invasive and invasive approaches and may lead to ICD implantation.

Asymptomatically affected family member:

This is, in practice, a frequent and a difficult question. Again non-invasive and (if accepted by the patient) invasive testing can identify the risk. However, we know that some cases are definitely at risk even if all the clinical data look satisfactory.

Asymptomatic non-affected family member:

Follow-up of these patients is recommended.

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