Published in final edited form as:

Am J Cardiol. 2014 May 15; 113(10): 1735–1739. doi:10.1016/j.amjcard.2014.03.001.

Arrhythmogenic Right Ventricular Dysplasia Back in Force

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Arrhythmogenic right ventricular dysplasia (ARVD) was first recognized in 1977 during a surgery to map and treat ventricular tachycardia at the Hôpital de La Salpêtrière.¹ We first found that the ventricular tachycardia originated from the right ventricle (RV) rather than the usual left ventricular scar regions. We then identified interesting but unexpected tiny signals during the epicardial mapping that consistently occurred after the end of each QRS complex on the surface electrocardiogram.¹ Later, similar signal was also observed as a slur at the end of right precordial QRS complexes, both were named epsilon wave. The name “epsilon wave” was given because (1) it is small in amplitude, (2) it is a “postexcitation” phenomenon that mirrors the “pre-excitation” delta wave at the beginning of each QRS complex, (3) it is the next Greek letter after delta, and (4) it probably represents delayed activations of right ventricular myofibers.²

Electrogenesis of epsilon wave was a big mystery back then. It was thought to be either the result of a functional abnormality like the long QT syndrome or because of a structural anomaly. Observations from gross pathology of ARVD hearts during surgeries and later from histologic pathologies of tissue samples taken at surgery proved that the second mechanism was correct. At that time and on 4 consecutive patients, we found a significant decrease in the RV myocardial thickness with only a thin, remaining subendocardial myocardial layer when the RV was opened by a “simple ventriculotomy.” This myocardial pathology in the RV was in sharp contrast to the exceedingly thick fat layers covering areas of RV with poor and abnormal contractions. Strands of surviving myocardium inside fat layers could be observed and sometimes connected to adjacent normal myocardium, likely accounting for zones of slow conduction and the electrogenesis of epsilon waves. However, conclusive clinical abnormalities were only obtained after the study of 24 young patients with resistant ventricular tachycardia, but a rather good left ventricular function many years after the ARVD name was given to this new clinical entity.³

In terms of naming this disease as ARVD, I was compelled to give a name to this Strange small group of patients when I was writing a book chapter reporting our surgical findings of this disease. After a long period of thinking, I decided that the term of dysplasia or dystrophy was most appropriate because these cardiac pathologies occurred mostly in young patients and were likely the result of abnormal postnatal development. Some years later, I discovered the article of Dr. Henry Uhl from the Johns Hopkins who reported in 1959 a

unique case of an 8-month-old girl who died from heart failure. In this article, this young infant girl had an extremely enlarged RV that was almost devoid of myocardium and was replaced by fibrosis with apposition of epicardium against endocardium, now commonly termed Uhl's anomaly. I was particularly pleased to read that Dr. Uhl also reached a similar conclusion that the strange RV anomaly in this infant girl was the result of a "trouble in development."⁴ However, it is now clear that the Uhl's anomaly is amore severe and early-onset disease process than ARVD. Dr. Thomas James discussed this concept from a pediatric case with major absence of the RV myocardium and suggested a phenomenon of cardiomyocyte apoptosis.⁵ This new advance in the pathogenesis of ARVD was finally demonstrated by our group in patients with ARVD.⁶

Of note, there were also other case reports describing cardiac abnormalities like ARVD in the early days. Waller et al examined the heart specimens of 2 adults who died from sudden death or heart failure, respectively, and showed a major decrease in the RV myocardium in these 2 hearts. They used the term "hypoplasia of the right ventricle" to describe the cardiac pathologies as part of the parchment heart syndrome. However, they presented only gross pathology with beautiful artistic drawings without fat and histologic correlates.⁷ Of particular interest, I also found a famous drawing of a human heart by Leonardo daVinci that depicts an enlarged and thin RV, similar to our description of ARVD hearts although not covered by fat (Figure 1).

In 1988, some workers of the pathology group at Padua reported ARVD-like pathologies in 12 of the 49 hearts of young adults who died suddenly, mostly during exertion, in the Veneto region.⁸ They observed a progressive loss of myocardium; lipomatous or fibrolipomatous replacement; and foci of inflammation, degeneration, and necrosis predominantly in the RV. Because cardiac pathologies in this young adult population were not previously reported and were considered as the result of an unknown mechanism, they used the term "right ventricular cardiomyopathy" to describe this disease category. The Padua groups later published further studies on this disease with a more detailed discussion in their reasons of not using the term "dysplasia" or "dystrophy" but "cardiomyopathy" to describe this disease entity.⁹ They considered that this disease is a heart muscle disorder and described 2 pathologic patterns of this disease: fatty and fibrofatty replacements of the RV myocardium with more inflammation in the fibrofatty subgroup. They concluded "In the fibrofatty variety of ARVC, the myocardial atrophy appears to be the consequence of acquired injury (myocyte death) and repair (fibrofatty replacement), mediated by patchy myocarditis." In an Internet meeting, Rampazzo geneticist from the same university wrote "Finally, the name 'dysplasia' was adopted because it was supposed that the alteration of myocardial tissue could be due to a developmental defect. On the contrary, now it is clear that such alterations are the end-stage of a slow degenerative process: therefore 'Cardiomyopathy' appears more appropriate." Because their descriptions and subsequent identification of desmosomal mutations as the main cause of this disease,¹⁰ ARVD is now commonly known as arrhythmogenic right ventricular cardiomyopathy (ARVC) or is termed with a more generalized name arrhythmogenic cardiomyopathy.

Because I am the original person to name this disease ARVD, I feel that I am compelled to discuss the pros and cons of using these terminologies to describe this unfortunate cardiac

disease entity. First, from the perspective of cardiac development, development of human cardiomyocytes is not just limited to the cardiac differentiation during embryogenesis. Human cardiomyocytes continue to develop, mature, and regenerate postnatally and only reach adult size at ages from 10 to 20 years.¹¹ Second, recent evidence suggests that ARVD/ARVC is a disease of cardiac progenitor cells,^{12,13} supporting our original proposal that ARVD is due to cardiac developmental defects. Thus, considering cardiac development and maturation continue to young adulthood, “dysplasia” remains a correct description of this disease.

In addition, the term “cardiomyopathy” may include too many different subtypes of diseased hearts with ARVD-like pathologies and render the search for a unified pathogenic mechanism and therapy very difficult, if not impossible. This is clearly demonstrated by the fact that only up to 50% of patients with ARVC have desmosomal mutations. Whether ARVC with desmosomal mutations is the same disease as the ARVC without desmosomal mutation remains unclear, and the treatment strategies for these 2 conditions may differ greatly. For instance, Saffitz’s group recently showed that the desmosomal protein downregulation could be found in granulomatous myocarditis that might account for their arrhythmogenesis.¹⁴ If the cause of the desmosomal dysfunction is inflammation associated with myocarditis, clinical therapy should be directed toward the treatment of inflammation rather than the correction of an inherited mutation. Recent disappointments in many clinical trials to find additional and novel therapy for all cardiomyopathies with heart failure strongly indicated the need to elucidate pathogenic mechanism and tailor novel therapy to a specific disease subtype.¹⁵ Therefore, with recent advances in genetic and stem cell research, now might be a right time to recategorize the patients with desmosomal mutations and RV pathologies to the original description as ARVD so that a potential therapy could be invented. For patients with ARVD-like pathologies but without desmosomal mutations, it might be feasible to categorize them as one of the multiple facets of ARVCs, so that therapies for a primary cause could be identified.¹⁶

Furthermore, from the pathologic standpoint, inflammation due to myocarditis can produce multifocal areas of adipocytes and fibrosis. Myocarditis can lead to various clinical and histologic patterns such as fulminant, acute, chronic, chronic-active, and completely healed (burnout) cardiac pathologies. However, histology of myocarditis extending from patchy areas of fibrosis and adipocytes to large areas of “replacement fibrosis” does not resemble the topographic lesions of ARVD. ARVD pathologies seen at low magnification (20×) suggest that this disease starts from the mediomural layers and extends mostly to the epicardium.^{17,18} This point deserves further discussion. Normal RV myocardium consists of 2 layers of myocardial fibers oriented in perpendicular directions. Myocardial fibers located at the junction between these 2 layers are interspersed and distorted. This is obviously an area of weakness that might sustain higher shearing forces during cardiac contraction. If a desmosomal mutation is present and weakens the cell-cell mechanical connection, this particular area will be vulnerable to mechanical damage and subsequent pathologies. This phenomenon may start during embryogenesis when the RV is systemic.¹⁶

Furthermore, and in contrast to the conclusion by the Padua’s article,⁸ Burke and Virmani demonstrated that there might be different pathogenic processes between the fatty and

fibrofatty patterns associated with ARVC.^{18,19} These authors were also the first to confirm our original observation that fat (without fibrosis) is also a component of a large number of so-called normal hearts (Figure 2).^{20,21} This point is not just an academic discussion because “adipositas cordis” can explain the unexpected occurrence of irreversible RV failure observed in a few days after a successful cardiac transplantation (Figure 3).²² This catastrophe occurs in around 12% of our patients (personal communication, Pr Daniel Duveau Nantes, France. October 2012).

Many animal models of ARVD have been established²³ and have led to novel pathogenic insights. One of the most exciting advances in elucidating the pathogenesis of ARVD is the recapitulation of “ARVD” cardiomyocyte pathologies in a dish using cardiomyocytes derived from patient-specific induced pluripotent stem cells with ARVD.^{13,24,25} All models used patients with ARVD with plakophilin-2 mutations. Both studies by Ma and Caspi et al showed that ARVD cardiomyocytes displayed aggressive lipogenesis under adipogenic conditions yet without cardiomyocyte apoptosis. Caspi et al had to use serum starvation to show the higher vulnerability of ARVD cardiomyocytes to apoptotic stress, but serum starvation is not a clinically relevant condition for ARVD. Of particular interest is the ARVD model published by the Chen’s group from San Diego.¹³ They applied hormones, steroids, adrenergic mimics, and oxidized low-density lipoprotein to recapitulate simultaneously aggressive cardiomyocyte apoptosis and lipogenesis, pathologic signatures of ARVD. All added factors in this study are analogues of endogenous hormones and factors in normal human blood, rendering the Chen’s model more clinically relevant. Also, they demonstrated that metabolic maturation during postnatal cardiac development is essential to establish the ARVD pathologic phenotypes, consistent with our original hypothesis in 1977 that ARVD is a disorder of cardiac development. More importantly, metabolic derangement in ARVD cardiomyocytes with abnormal peroxisome proliferator-activated receptor gamma activation is the key pathogenic mechanism. Inhibition of abnormal peroxisome proliferator-activated receptor gamma activation can prevent all ARVD pathologies, and the elimination of radical oxygen species can reduce apoptosis of ARVD cardiomyocytes. Of note, our research group at the Hôpital de La Salpêtrière was the first to report the abnormally high peroxisome proliferator-activated receptor gamma levels in the RV tissue samples of human ARVD hearts.²⁶ Therefore, I am glad to see that the establishment, evolution, pathogenic findings, and potential therapies of ARVD finally run a full circle, back to where the disease was identified. I must say that the “force” of “dysplasia” remains strong.

Not completely understood at this time is how environmental and inflammatory factors affect or modify the clinical manifestations of ARVD with genetic mutations, which had been pointed out by Basso et al⁹ “Whether the inflammation is a primary event or a reaction to spontaneous cell death remains unclear.” For instance, inflammation can be a cofactor of morbidity and mortality, which I have seen at the end stage of ARVD. This phenomenon was finally confirmed by autopsy or heart samples during heart transplant. The same concept can be extended to all the other forms of cardiomyopathies.²⁷ Moreover, recent advances in techniques of time-of-flight mass spectroscopy have made rapid identification of viral causes of ARVC possible.²⁸ Also, biventricular endocardial biopsy is now a safe procedure, provided that a strict protocol is followed.^{29,30} These technical advances presumably can lead to a specific antiviral treatment such as interferon beta.³¹

Sarcoidosis of the heart, like ARVD, is rare.³² However, the combination of these 2 entities is not rare in my experience. It has been said that sarcoidosis can masquerade clinically as ARVC because of desmosomal downregulation for this particular granulomatous inflammatory disease.¹⁴ However, I must point out that sarcoidosis can be superimposed on ARVD. The reason why sarcoidosis has not been previously associated with altered desmosomal proteins is likely that pathologists observing the pathognomonic granulomatous pattern are satisfied to establish the diagnosis of sarcoidosis without paying attention to the particular histologic structure of desmosomes, which requires additional immunostaining. In addition, I have seen several cases of lymphocytic myocarditis superimposed on ARVD generally explaining major LV dysfunction and the final irreversible outcome. Common enteroviral viruses have been reported in ARVD as well.³³

In a recent pathologic review, Dr. Roberts concluded that, after reviewing these previously neglected dysplasia/cardiomyopathies, despite it was not perfect, the term of dysplasia has been used extensively during around 30 years and is probably here to stay.³⁴ Dr. Chen's group put ARVD back in force after being able to beautifully reproduce the "trouble in development" in a dish.¹³ This stem cell-based approach is a new tool that might lead to novel therapies for ARVD hearts with desmosomal mutations. Hopefully, with these ARVD models in a dish, we will identify drugs or small molecules that are capable of slowing or preventing disease progression. Clinicians will then be able to use novel therapies to block disease progression in addition to the existing heart failure and antiarrhythmic medications as well as implanted cardiac defibrillator and ablation for arrhythmia controls.³⁵ More importantly, to prevent ARVD progression, we must stress the need for early detection of the disease by biomarkers or advanced technologies, such as electrocardiogram technologies that are capable of extracting delayed potentials inside the QRS complexes, which are promising noninvasive techniques (J.J. Schmid, R&D Director of Schiller Company, personal communication, December 2013).

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Figure 1.
This sanguine by Leonardo da Vinci is impressive by the enlargement and the thinness of RV.

Figure 2.

Score of fat in the RV from 82 patients aged 15 to 75 years old, who died from a noncardiac cause in a general hospital of Paris (Dr. Fabrice Fontaliran study). Quiescent right ventricular dysplasia observed in 4% of this study showed the same amount of fat than the score IV plus interstitial fibrosis. Fat dissociation syndrome has occasionally been called less precisely as coradiposum or adipositas cordis because cover of pure fat on epicardium remains within normal limits. However, rupture during acute myocardial infarction is more common in the fatty heart than in the nonfatty heart (Roberts WC and Roberts JD36).

Figure 3. Irreversible RV failure after heart transplantation. RV myocardium mostly replaced by fat without fibrosis. (20 Sirius Red staining, courtesy of Pr Paul Fornes, Paris).