Arrhythmogenic Right Ventricular Dysplasia Back in Force

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]

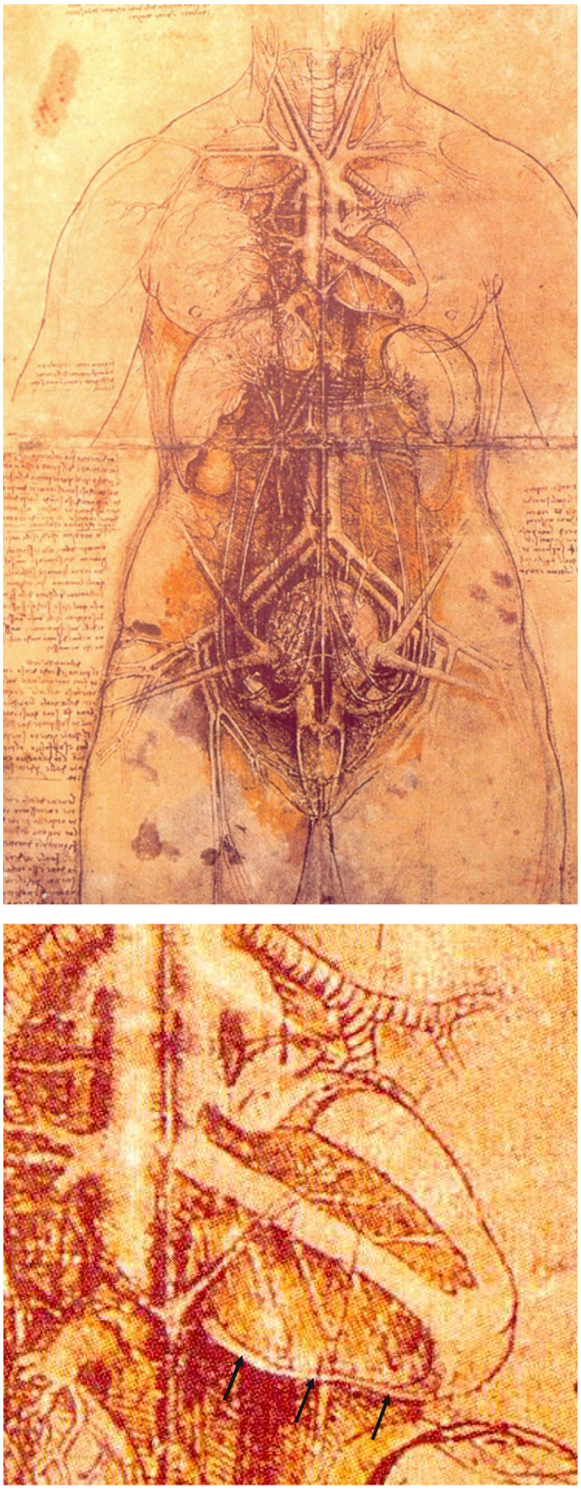

Figure 1. This sanguine by Leonardo da Vinci is impressive by the enlargement and the thinness of RV.

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 a more severe and early-onset disease process

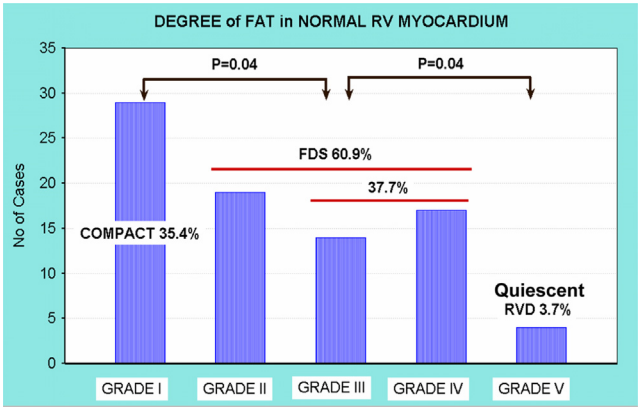

Figure 2. Score of fat in the RV from 82 patients aged 15 to 75 years old, who died from a noncardiac cause in a general hospital of Paris (Dr. Fabrice Fontaliran study). Quiescent right ventricular dysplasia observed in 4% of this study showed the same amount of fat than the score IV plus interstitial fibrosis. Fat dissociation syndrome has occasionally been called less precisely as cor adiposum 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 JD[36]).

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 da Vinci 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