Arrhythmogenic Right Ventricular Cardiomyopathies
Clinical Forms and Main Differential Diagnoses

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In this issue of Circulation, Burke et al report the results of a morphological and morphometric analysis of RV myocardium to differentiate fatty infiltration of the RV free wall from fibrofatty infiltration, which is the histological marker of ARVC. A similar analysis was previously presented by Thiene et al, classifying their patients as having “lipomatous” as opposed to “fibrolipomatous” replacement of the myocardium and putting the two entities in the same group. Unless small areas of fibrosis are overlooked, the two subgroups of Burke et al and Thiene et al have the histological picture of myocardium intermingled with and/or replaced by fat without associated fibrosis. In this population of patients who died suddenly, we are faced with the observation that strands of myocardial fibers within fat without fibrosis may lead to sudden death. This possibility has rather important consequences, because a large proportion of seemingly normal hearts have fatty infiltration of the RV myocardium. It may be that the fatty pattern in these patients represents the early stage of the disease before the appearance of fibrotic tissue. Therefore, a large proportion of normal individuals may in fact have the prerequisite for the development of RV cardiomyopathies.

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It is well known that a large majority of patients with ARVD have histological evidence suggestive of inflammation. It may be that if myocarditis is superimposed on the background of myocardium interspersed by fat, strands of cardiomyocytes involved in myocarditis will produce fibrosis and will transform the purely fatty to the fibrofatty form. Activation of neutrophils induced by myocarditis will enhance the risk of arrhythmogenesis. Therefore, the two groups identified by Burke et al may represent two consecutive stages of myocardial disease progression.

It is possible that multiple attacks of myocarditis could lead to the destruction of an increasing number of myocardial cells involving both the right and the left ventricles, causing irreversible heart failure that is similar to the pathological findings of end-stage dilated cardiomyopathies. If the additional factor of an abnormal host immune response is involved, this could lead to an autoimmune phenomenon, accelerating myocardial dysfunction. Therefore, the new group of cardiomyopathies recently introduced in the WHO classification encompasses a wide spectrum of diseases that have the same basic histological structure but may have different clinical presentations and outcomes. On the basis of these concepts as well as the probable mechanism of adipogenesis, we propose a classification of ARVCs based on our current experience of >250 patients and 72 histological samples collected during a period of 23 years in France and 7 other countries, including the United States, Japan, and Australia.

Isolated RV Dysplasia

Pure Form of ARVD

The macroscopic pattern of ARVD consists of dilatation of the right ventricle with bulges located in the infundibular, apical, and subtricuspid areas (the triangle of dysplasia). Most of the RV muscle is replaced by fat.

The typical histological pattern of ARVD consists of replacement of midmural and/or external layers of RV myocardium (and to a much lesser extent, LV myocardium) by fatty tissue and fibrosis bordering or embedding strands or sheets of cardiomyocytes. Thickening of the media of distal coronary vessels, which may explain atypical chest pain observed in these patients, is another marker of the disease (syndrome X?).

ARVD appears to be the result of a genetically determined abnormality of development observed early in life, possibly even in the embryo, as the possible result of a mutation in the dHAND transcription factor, mostly controlling RV development. We have observed infiltration of myocardium by fat without fibrosis or inflammatory signs in a 27-week-old fetus that was brought to our attention because of RV aneurysm and arrhythmias observed in utero (Figure). Few pediatric cases of ARVD have been reported. After a phase of latency in which only ECG signs may be present, the early clinical manifestation is usually that of ventricular arrhythmias originating in the right ventricle, observed during adolescence and in early adulthood. In some cases, sudden death is the first presenting symptom of the disease. With conventional unguided drug treatment, the incidence of sudden death is 1% per year.

Because of minor involvement of the left ventricle, LV failure is not observed. In some cases, RV failure could be the result of severe progression of the original dysplastic phenomenon in the right ventricle.

Naxos Disease

The Naxos disease is a form of ARVD, which has been observed on the island of Naxos, Greece; it involves 25 patients from 12 families. It is an inherited condition with a recessive form of
Selected Abbreviations and Acronyms

ARVC = arrhythmogenic right ventricular cardiomyopathy
ARVD = arrhythmogenic right ventricular dysplasia
LV = left ventricular
PVC = premature ventricular contraction
RV = right ventricular
WHO = World Health Organization

transmission and a familial penetrance of 90%. It is associated with another dysplasia, palmoplantar keratosis. Clinical signs, ECGs, and biopsies are consistent with ARVD. Clustering of the disease on this island may have resulted from inbreeding that occurred in the same manner as that observed in south Suffolk with familial cardiomegaly.

Venetian Cardiomyopathy

Venetian cardiomyopathy (originally called RV cardiomyopathy) has most of the clinicopathological presentations of ARVD, but the familial incidence reaches a level of 50% in the Veneto region, as opposed to no more than 15% to 25% in other series. The degree of familial penetrance is less than in Naxos disease. Of interest is that the island of Naxos was occupied twice by Venetian merchants. Our case of ARVD diagnosed in utero was from the Veneto region. The youngest patient with ARVD who died suddenly at age 7 was of Italian descent. There are also an increased number of sudden deaths in family members, patients from three generations, and a larger number of patients with LV involvement.

Noncoronary RV Precordial ST-Segment Elevation

This syndrome has been observed in young adults who have a risk of sudden death during rest or sleep. Some patients with the typical ECG findings of this condition have ARVD. Sudden death during sleep observed in young males with intermittent ST-segment elevation, reported in South East Asia, may pertain to the same condition. However, no pathological examination of the RV free wall is currently available. However, some cases of Pokkuri disease described in Japan are also histologically proven examples of ARVD.

RV Outflow Tract Tachycardia

RV outflow tract tachycardia patients studied by MRI show signs of structural heart disease. This was confirmed in some cases by contrast angiography, strongly suggesting the presence of ARVD localized to the infundibular area. However, other arrhythmogenic substrates have been suggested, but the prevalence of ARVD cases in this group needs further study.

Benign Extrasystoles

Benign extrasystoles have a pattern suggesting an infundibular origin. Patients with outflow tract ventricular tachycardia may have the same QRS morphology. Therefore, it is not surprising that some patients who have PVCs of this morphology may have ARVD. We recently observed a teenage patient who had PVCs arising from the infundibulum. She was resuscitated from cardiac arrest but finally died of irreversible brain damage. The histological pattern of ARVD was associated with an exceedingly large amount of interstitial fibrous tissue in the infundibular area associated with inflammatory reaction. We think, however, that the cause of death was more probably related to myocarditis than a histological pattern of dysplasia localized to the infundibulum.

Uhl's Anomaly

This extremely rare anomaly falls into two age groups and has a clearly distinctive clinical as well as pathological presentation. Uhl's anomaly generally leads to congestive cardiac failure at an early age and death after a few weeks or months. In the adult age group, death is either the result of congestive heart failure and/or cardiac arrhythmias. Uhl's anomaly shows the striking and unmistakable pattern of a huge and transparent RV free wall. This is the result of apposition of the endocardium with the epicardium with some fatty tissue but without intervening myocardium. In some

Evidence of right lateral aneurysm of a 27-week-old fetal heart, arrhythmogenic in utero. Histology shows evidence of adipocytes interspersed with myocardial fibers. Neither fibrosis nor signs of inflammation were observed. Hematoxylin-phloxine-saffron stain; magnification X400.
cases, the anomaly is limited to a small zone of the RV free wall and may be discovered by chance at autopsy.

It has been suggested recently that Uhl’s anomaly and ARVD share a similar pathogenesis. Uhl’s anomaly appears to be the result of an extensive and complete apoptotic destruction of RV myocardium as opposed to ARVD that may be due to a localized transient phenomenon progressing over a long period of time.35

Mitral Valve Prolapse
A systematic pathological study of sudden death patients with clinically suspected or autopsy-discovered mitral valve prolapse from the Veneto region of Italy showed that two thirds of these patients had the RV histological substrate of ARVD.26 This finding may explain the inconsistencies in the results of surgical replacement of the mitral valve for the prevention of arrhythmias and sudden death in patients with mitral valve prolapse.27 However, as with the Venetian cardiomyopathy, it is necessary to consider the possibility of disease clustering in the area of the world from which this report originates.

Nonarrhythmogenic Forms of ARVD
The new WHO classification has included the term “arrhythmogenic” in ARVC. However, cardiac arrhythmias are an epiphénomeron, and some patients with a clear-cut pattern of ARVD discovered by invasive or noninvasive tests of the RV myocardium do not have ventricular arrhythmias. In those patients, the arrhythmogenic substrate is present but silent. These patients may have ECG signs of ARVD and late potentials detected by signal averaging. This could explain false-positive results observed in some apparently normal individuals.

Dysplasia With Major LV Involvement
Biventricular Dysplasia
Pure Biventricular Dysplasia
This form is characterized by the same disease process involving the left as well as the right ventricle. The typical histological structure is observed in the LV free wall, which is replaced by fatty tissue, and there should be strands of cardiomyocytes embedded in or bordered by fibrosis. Biventricular dysplasia can lead to cardiac insufficiency because of excessive loss of LV myocardial tissue and may be wrongly diagnosed as idiopathic dilated cardiomyopathy.28 However, identification of infiltration of the left ventricle by fat should lead to the correct diagnosis.

Dysplasia Complicated by Myocarditis
Dysplasia may also be complicated by a large amount of inflammatory reaction in a small percentage of patients. In this case, both ventricles are generally involved, and the prognosis is poor.29 Because only a small number of patients with ARVD have no inflammatory infiltrates, it may be deduced that myocarditis is probably superimposed on the genetically determined structural background of ARVD. A striking demonstration of this concept is the study of identical twins with completely different evolution, suggesting both familial and environmental factors.30

The term “myocarditis” is used to indicate a histological picture consistent with acute inflammation. This inflammatory process may be the result of multiple causes (viral, bacterial, fungal, toxic, autoimmune, etc), it may be localized or diffuse, and it may be observed at different stages of evolution. It may also be associated with a wide spectrum of clinical manifestations ranging from absence of symptoms and complete resolution to death within a few days.31

It is commonly accepted that patients with structural heart disease are more sensitive than normal individuals to myocarditis, and the two recent analyses of sudden death in athletes in whom myocarditis has been identified strongly support this hypothesis.32,33

When myocarditis involves both ventricles, congestive heart failure can cause death in an additional 1% of patients per year. At a late stage of the disease, it is difficult to distinguish ARVD from an advanced form of idiopathic dilated cardiomyopathy.5

The diagnosis of ARVD is even more difficult in cases of myocarditis complicating the nonarrhythmogenic form. Therefore, patients with RV dysplasia could present with a clinical overt or concealed myocarditis and a clinical evolution consistent with idiopathic dilated cardiomyopathy. Microscopic histological examination of the RV free wall will show the pattern of dysplasia. However, this diagnosis could be obscured by the signs of myocarditis and may escape attention if not specifically looked for.34

We have reported one case of fulminating heart failure due to catastrophic myocarditis superimposed on the background of typical ARVD and another case of long-term evolution of LV dysfunction resulting in death with a typical pattern of ARVD on the right side of the heart and chronic progressing myocarditis on the left.11,34

Differential Diagnosis
Idiopathic Dilated Cardiomyopathy
Idiopathic dilated cardiomyopathy at an early stage of the disease when there is still some preservation of LV function with ventricular tachycardia originating from the right ventricle may be mistaken for ARVD. However, cardiac imaging will demonstrate global dilatation and hypokinesia of both ventricles, as opposed to the segmental abnormalities that are a typical feature of arrhythmogenic RV dysplasia.35

Isolated Myocarditis
The histological diagnosis in most of these cases is unmistakable, but it could be confusing when myocarditis results in a large number of adipocytes. However, the topographic distribution of fat will not be similar to ARVD.

Pure myocarditis could be by itself arrhythmogenic, both during its acute phase and after its complete healing. This has recently been confirmed in cases of sudden death during sports.32,33

Adipomatosis Cordis or Cor Adiposum
This form, discovered by chance at autopsy, looks like biventricular dysplasia, with a continuous layer of fatty tissue covering both ventricles.36 There are no ventricular arrhythmias. However, the distinction from ARVD is that this form typically has no fibers embedded in fat on either the right or the left ventricle.
Conclusions

The polymorphism and wide clinical spectrum of ARVCs in general appears to be the result of one and possibly two basic characteristics of the heart musculature of the human species: replacement of myocardium by fat and susceptibility to environmental factors. These features could be a contributing factor in many causes of death. Without properly assessed pathological data, it is impossible to estimate their real significance in the population at large. However, it is certain that ARVCs are much more frequent than previously recognized. In addition, greater knowledge of ARVCs will help to understand other cardiomyopathies. Therefore, enrollment of cases in an international registry of patients with ARVC could enhance the proper identification and understanding of multiple diseases of the myocardium and will stimulate both basic and clinical research. Registries for ARVC have now been established both in the United States and in Europe.

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References

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