The multiple facets of right ventricular cardiomyopathies

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This editorial refers to ‘Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry’, by B. Pinamonti et al., on page 1105 and ‘Arrhythmogenic right ventricular cardiomyopathy/dysplasia on the basis of the revised diagnostic criteria in affected families with desmosomal mutations’, by N. Protonotarios et al., on page 1097

Arrhythmogenic right ventricular dysplasia (ARVD) was the term originally used to identify a new cardiac entity characterized by right ventricular arrhythmias and juvenile sudden death. Recognition of this disease was the result of the investigation of a group of patients who had no cardiac abnormalities on physical examination but developed episodic right ventricular tachycardia. Treatment by open chest ventriculotomy was successful in preventing recurrent ventricular tachycardia. Other terminology has subsequently been used to describe this disease, including ARVC/D, which was included in the new classification of cardiomyopathies in 1996. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is also employed to describe this entity. The original term of arrhythmogenic right ventricular dysplasia (or dystrophy) was chosen because sections of the right ventricle during surgery showed a marked decrease in muscle thickness covered by a large amount of fat, suggesting a defect in development. This inference was also made by Henry Uhl in his description of his eponym case. It was impossible for pathologists to identify the disease with certainty because fat without fibrosis is frequently observed in the free wall of the right ventricle, a feature unique to the human species. Due to advances in molecular biology, this developmental defect consisting of an increased amount of adipocytes and interstitial fibrosis replacing cardiomyocytes starting in the embryo (Figure 1) and progressing during adolescence and adulthood has been partially elucidated. This pathological process may produce sustained ventricular arrhythmias. Atrial arrhythmias can also be the first presentation of the disease, suggesting a more generalized cardiomyopathy. Subsequently, other entities have been included that primarily affect the right ventricle, such as some cases of Brugada syndrome or some cases of right ventricular outflow tract tachycardia, in addition to Uhl’s anomaly and Naxos disease, resulting in a wide spectrum of right ventricular cardiomyopathies. However, right ventricular outflow tract tachycardia and right ventricular dysplasia remain the most common forms of right ventricular cardiomyopathies. Some patients with ARVD treated with antiarrhythmic drugs and/or an implantable defibrillator may have an uneventful course over decades. More frequently, over a long-term follow-up there is progressive right ventricular enlargement as well as a later expression of left ventricular disease. An

Figure 1 Embryology of arrhythmogenic right ventricular cardiomyopathy/dysplasia

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increasing number of our patients develop major congestive heart failure leading to death. This outcome can be precipitated by signs of inflammation of unclear origin involving both ventricles. The possible causes of inflammation include genetically determined susceptibility to myocarditis.

The work of Pinamonti et al. describes a detailed evaluation of the prognosis of a large series of patients with ARVC. These authors confirm that ARVC leads to irreversible heart failure in a significant portion of patients. Analysis of this cohort utilizes algorithms developed over years in the study of heart failure and dilated cardiomyopathies. The authors are the first to stress that tricuspid regurgitation appears to be a new and important prognostic factor in ARVC.

Not discussed by Pinamonti are patients with suspected ARVC that progress to left ventricular failure with only minor or even no arrhythmias. The phenotype of these patients can be pure cardiac failure leading to death or heart transplantation, and the correct diagnosis is made only after careful pathological examination. There are several possible mechanisms of left ventricular involvement. The first is related to the presence of the same disease process of cell–cell junction abnormality as well as fibrofatty replacement of myocardium involving both ventricles from the early stage of the disease. This condition is called ‘biventricular dysplasia’, which can be detected by cardiac magnetic resonance (CMR) imaging. It shows the typical pattern of fat in the left ventricle in addition to the right ventricle. Another possible cause of left ventricular functional impairment could be due to the progression of severe dilatation of the right ventricle, which compresses the left ventricle, leading to a decrease in left ventricular ejection fraction. These cases may need anticoagulation to prevent formation of right ventricular clots. In addition, consideration should be given to decreasing the extent of right ventricular dilatation when the left ventricular ejection fraction is <35% in the presence or absence of severe right ventricular dilatation. Anterior cardiomyoplasty with fixation of the lower part of the latissimus dorsi on the diaphragm has been proposed to treat these patients, and favourable results have been observed. In particular, all of our seven patients with this scenario improved from American Heart Association functional Class III to functional Class II. Also, ventricular arrhythmias decreased and, in some cases, disappeared completely after several months, probably because of a decrease of the stretched myocardial fibres, a well-established determinant of cardiac arrhythmias. However, stimulation of the latissimus dorsi with every other beat does not increase transmural flow. Therefore, a nest covering the entire heart may produce the same result, but this approach has not yet been performed.

It is striking to observe severe fibrosis and lymphocytic infiltration in both left and right ventricles in some patients with severe congestive heart failure due to ARVD. This suggests the possible role of inflammation of unclear mechanism. This can be associated with abrupt acceleration of biventricular cardiac failure that leads to the hypothesis that ARVD is a genetic disease in which environmental factors can trigger heart failure as well as a surge of ventricular arrhythmias.

If myocarditis is involved, there may be a wide spectrum of presentation, ranging from years of silent deterioration of cardiac function with, at the other extreme, fulminant myocarditis leading to hyperacute heart failure. We reported a case of a woman who developed signs of acute myocarditis and died within a few days of severe heart failure. The most impressive cases that we have observed are from a family in which three children developed high fever and died of acute heart failure. The aetiology was unknown for the first child; ARVD with signs of inflammation was suspected at autopsy in the second, and was definitely proven in the third child in whom left ventricular ejection fraction decreased from almost normal to irreversible heart failure within 16 h. When properly diagnosed, these patients can be treated by cardiac pump assist for several weeks until they recover left ventricular function. Impressive results have been recorded.

The history of the discovery of Naxos disease started by the referral to our centre of two patients with recurrent ventricular tachycardia who showed clinical evidence of ARVD by ECG and echocardiography. However, these patients had the unusual finding of palmoplantar keratoderma. The disease had a familial pattern suggesting a recessive form of transmission. I was convinced that it was due to a genetic abnormality. I suggested that Dr Protonotarios contact Dr McKenna from London. Dr McKenna and associates identified the abnormal chromosome and later the first mutation on a desmosomal protein. This was the beginning of the discovery of many other candidate genes on adjacent molecules in the typical forms of ARVD.

Dr Protonotarios observed that, in his experience, acute episodes of ventricular tachycardia were preceded by general signs of inflammation probably of a viral origin. This was evident in his population probably because the Naxos disease patients are homozygous and both parents are affected. This led to the identification of some of the viruses involved in this pathology. Recently we have reported an increase of C-reactive protein in patients who have recent ventricular tachycardia as compared with ARVD patients referred without arrhythmias. Nevertheless, the link between inflammation and arrhythmias is still unclear. Of interest is the observation by Hoffman et al. that inflammation may lead to the production of early after depolarizations which may be a mechanism for ventricular arrhythmias. Now Protonotarios et al. report improvement of sensitivity by the new International Task Force Criteria. In my view, the main value of the new criteria are that they are based on numeric comparisons with normal parameters provided by a control group so that abnormal relevant right heart abnormalities can be detected with confidence.

Protonotarios also stresses the role of the ECG for the detection of the disease. We need to investigate subtle but probably important abnormalities in the ECG including changes in the rate of depolarization of the QRS complexes. This may be diagnostically useful particularly in patients suspected of ARVD with normal physical examination. A combination of these slight but possibly important abnormalities in addition to T-wave inversion leads to the diagnosis of ARVD in the hundreds of cases of our patients with definite ARVD. After the completion of this study, one patient was observed in whom the ECG was normal but late potentials were nevertheless discovered by signal averaging. This new concept of QRS fragmentation was evaluated in a prospective international multicentre study that confirmed the
increased sensitivity (85%) of detection of ARVD by analysis of the fragmentation of the standard 12-lead ECG. If the findings from this study were combined with T-wave inversion, it is probable that they would have found a further increase in sensitivity. Nevertheless, the value of this approach in the overall population is unknown. A marked increase in sensitivity could lead to a loss of specificity. The main differential diagnosis appears to be a sequel of focal myocarditis which may explain QRS complex fragmentation sometimes observed in one or more pre-cordial leads. In a series of 30 000 ECGs recorded in young conscripts, 78 had abnormalities. In three a diagnosis of a quiescent severe form of ARVD was suspected, and 20 had less evident signs which could be due to common ARVD or a sequel of myocarditis (G.F. unpublished data).

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**References**

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