The Mystery of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy
From Observation to Mechanistic Explanation

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Only 24 years have elapsed from the time that the clinical profile of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) was first described. Since then, this entity has been found to have a prevalence of about 1 in 5000 persons and is well recognized in the United States, Europe, and Asia. The usual clinical presentation of ARVD/C is that of palpitations, nonsustained ventricular tachycardia, and sustained ventricular arrhythmias. Uncommonly, sudden cardiac death may be the first manifestation of the disease. Most patients with this condition experience the onset of these symptoms between the ages of 20 and 40 years, and the disease shows a predisposition to occur in men. A familial incidence was noted in the early description of the disease.

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Certain observations about the disease were intriguing but puzzling. Why did there appear to be a striking incidence of athletic individuals affected by this disease? Why is there a predilection for the disease to primarily affect certain locations of the right ventricle: the right ventricular outflow tract, the apex, and the subtricuspid area of the right ventricle, the so-called “triangle of dysplasia”? Why is there a latent period for the development of the clinical manifestations of ARVD/C, because it is seldom evident in childhood but is expressed in late puberty, adolescence, or early adulthood?

Over the past 10 years, genetic studies have begun to unravel the mysteries underlying ARVD/C and to provide answers to these puzzling observations. In 2000, Bowles and Towbin predicted that there would be a “final common pathway,” the disruption of which leads to clinical disease development. We now know that ARVD/C is a disease of desmosomal dysfunction. Desmosomes are a family of proteins that include junctional plakoglobin, plakophilin, desmoplanin, desmoglein, and desmocollin, the function of which is to bind the myocardial cells to one another. Desmosomes provide cellular contact that is necessary for electric conduction and mechanical contraction of the myocardial cells. Once the molecular and structural defects started to become known, the pieces of the puzzle began to fit together.

It appears that it takes years and many hundred of thousands of myocardial contractions and mechanical stress forces to gradually disrupt myocardial cells. The right ventricular wall is thinner than the wall of the left ventricle and is therefore more vulnerable to cellular disruption. The thinnest parts of the right ventricle are located in the most vulnerable areas, the “triangle of dysplasia.” Sports activities, particularly running and bicycling, produce an increased frequency and vigor of contraction, which facilitate the disruption of the myocardial cells at an earlier age. In addition, the left and right ventricles respond differently to prolonged, vigorous exercise: The left ventricular size is reduced but the right ventricular size increases. Further evidence for the adverse effect of exercise on the phenotypic expression of ARVD/C was provided by Daubert et al, who found that individuals with ARVD/C who performed intensive and regular sports activities had symptoms at a younger age and that palpitations, syncope, and sudden death were more frequent in the athletic group than in patients with ARVD/C who were not athletically inclined. This may also explain why some members of a family who have a genetic defect of the desmosome but are not athletic may have no phenotypic expression of the disease.

These logical observations and deductions have been substantiated in part in the study reported by Kirchhof and associates in this issue of Circulation. In this study, the authors created heterozygous plakoglobin-deficient mice and compared these mice with age- and sex-matched control littermates. The animals were grouped into those that swam daily for 10 months and controls that did not. Endurance training accelerated the development of right ventricular dysfunction and facilitated the appearance of right ventricular arrhythmias in the exercised mice. From this experimental model, partial support for the observations noted above has been gained. However, several important issues are raised by this work. First, the clinical phenotype of the heterozygous plakoglobin-deficient mutant mouse has only limited similarity to the human forms of ARVD/C. In fact, none of the mutant mice were found to have myocardial fibrosis or fibrofatty replacement of cardiomyocytes, and only inconsistent right ventricular dilation was noted. The findings most similar to human ARVD/C were the ventricular arrhythmias and electrophysiological abnormalities. The ultrastructure of the desmosome and intercalated disks was normal in the mutants as well, irrespective of exercise. Furthermore, although some changes did occur in the myo-
cardium of mutant mice that were “endurance trained” by swimming over time, these changes were only mild, even in mice >10 months of age. Hence, it would be difficult to make sweeping correlations between the heterozygous plakoglobin mutant mouse model and the human condition. Although it is logical, the concept that exercise (endurance training) is harmful for patients at risk of developing ARVD/C and those with fully developed disease needs confirmation. The present study supports but does not conclusively confirm the hypothesis that endurance training aggravates the clinical disease process. We agree with the view expressed by Kirchhof et al.8 that further studies are needed to elucidate the relation between functional and structural changes in different models and populations affected by ARVD/C. We need more data before making mechanistic and treatment decisions for patients based on this work. Recent desmoplakin mutant mouse models have shown histological, pathological, ultrastructural, and clinical abnormalities similar to those of humans with ARVD/C.9 The next logical step would be to determine whether pharmacological agents can delay or prevent the right ventricular disease from becoming manifest in these models.

The answers to the puzzle that have been found in this and other recent work have emerged through collaboration between clinicians and basic scientists using a translational biology approach. This collaboration is gratifying, because the clinical and basic genetic information, coupled with the experimental data in animals, appears to be leading to ways to prevent the phenotypic expression of this disease. The ultimate challenge is to learn how to diagnose individuals who have early signs and symptoms of ARVD/C but do not have a family history, thus preventing the progression of the disease and allowing these individuals to live a normal life with ARVD/C. In addition, understanding the true mechanistic basis of ARVD/C could enable the development of targeted therapies for those patients who have already developed this life-threatening disease. The work by Kirchhof and colleagues helps to bring us another step closer to better understanding this disease and, we hope, to saving lives.

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References

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