A rrhythmogenic right ventricular cardiomyopathy (ARVC) is not a common disease, but it is a deadly one. A detailed understanding of its pathogenesis could provide insights into fundamental mechanisms pertinent to much more common cardiac conditions associated with sudden death. There are several reasons why this might be so. First, ARVC is the most arrhythmogenic form of heart disease in humans. The rate of appropriate shocks in patients with ARVC and implantable defibrillators far exceeds that rate in patients with other highly arrhythmogenic diseases such as long-QT syndrome or hypertrophic cardiomyopathy (data from the North American ARVC registry). Second, arrhythmias are a cardinal feature of ARVC and typically appear early in the disease before significant structural remodeling of the myocardium and contractile dysfunction develop. In this sense, ARVC may be as much akin to the ion channelopathies (arrhythmias in a structurally normal heart) as to other types of cardiomyopathies associated with sudden death, such as idiopathic dilated cardiomyopathy or hypertrophic cardiomyopathy in which arrhythmias typically develop in hearts with considerable structural and functional derangements. This does not mean that fibrofatty replacement of the right ventricle plays no role in sudden death. Tissue remodeling in ARVC undoubtedly contributes to arrhythmia substrates, but there is also something about the “unaffected” myocardium that seems to make this such an arrhythmogenic disease. Third, ARVC is a familial disease, usually inherited in an autosomal dominant pattern. However, genetic penetrance and disease expression are highly variable. It is not unusual for individuals who carry the same disease-causing mutation to have markedly different clinical manifestations. Even within families, a proband may die suddenly at a young age, whereas first-degree relatives with the same mutation can have a far more benign course. Knowing the monogenic causes certainly focuses attention on specific genes and provides an entry point into studies of disease pathways. However, there must also be powerful genetic modifiers, which ultimately determine the risk of arrhythmogenesis.

Identifying these modifiers and defining their modes of action could present new therapeutic targets and strategies to prevent sudden death not only in ARVC but also, perhaps, in more common forms of heart disease. This would be a welcome advance in a field that has long suffered a woeful lack of mechanism-based therapies.

**Article see p 418 and 428**

Understanding the genetic basis of ARVC has been challenging. Initial efforts used mapping approaches to identify chromosome loci in which disease-causing mutations were thought to reside. However, identifying the mutant genes and proving that these caused the disease have been difficult, in part, because the penetrance is so variable, and deciding which family members are affected can be fraught with difficulty. Indeed, early success came from identifying mutations in recessive cardiocutaneous syndromes such as Naxos disease or Carvajal syndrome in which ARVC (or something resembling ARVC) is a prominent feature, and penetrance is virtually 100%. These studies identified truncations in plakoglobin (Naxos disease) and desmoplakin (Carvajal syndrome), members of the catenin and plakin families of proteins that reside within cell-cell adhesion junctions known as desmosomes. Thus, the era of desmosomal mutations as causes of ARVC was launched and with it came the candidate gene approach in which probands and family members could be screened for mutations in all known desmosomal protein genes. On the one hand, this approach has been highly informative and has certainly advanced our understanding of disease pathogenesis by focusing attention on the desmosome. On the other hand, we are only seeing a part of the picture and perhaps a small part at best. This dichotomy is well illustrated in 2 articles appearing in this issue of *Circulation Cardiovascular Genetics*.

Two leading groups, from Johns Hopkins and the Netherlands, report on their efforts to identify and catalog desmosomal mutations in North American and Dutch patients with ARVC. The Hopkins group undertook a comprehensive analysis of desmosome mutations in 100 North American whites with clinically confirmed or suspected ARVC. They performed a sequence analysis on 5 desmosomal genes including those encoding the desmosomal cadherins desmoglein-2 (DSG2) and desmocollin-2 (DSC2), which span the membranes of neighboring cardiac myocytes and physically connect them by binding in the extracellular space, and the intracellular linker proteins plakophilin-2 (PKP2), desmoplakin (DSP), and plakoglobin (JUP), which bind the adhesion molecules to desmin intermediate filaments of the
cytoskeleton. The analysis included 82 individuals in whom ARVC was firmly established through an extensive analysis in which multiple diagnostic criteria defined by an international task force9 were fulfilled. The remaining 18 individuals were suspected of having ARVC but did not meet the task force criteria. A desmosome mutation (or at least a sequence variant not observed in controls) was found in 52% of patients with documented disease. In contrast, a mutation was identified in only 28% of patients with suspected ARVC. A majority of the observed mutations occurred in PKP2. Six individuals had >1 desmosomal gene mutation including examples of compound heterozygosity (2 different mutations in the same gene) and digenic heterozygosity (heterozygosity in 2 different genes). One individual had 3 mutations (although it was not clear that any single mutation was by itself sufficient to cause disease). Patients with a desmosome mutation were more likely to have experienced ventricular tachycardia than those without a mutation, but this is perhaps not surprising in view of the fact that ventricular tachycardia is a major diagnostic criterion, and individuals who experienced arrhythmias were more likely to come to medical attention (selection bias).

The multicenter study from 4 university hospitals in the Netherlands was designed to evaluate the prevalence and type of mutations in the desmosomal genes PKP2, DSG2, and DSC2 in a Dutch cohort of patients with ARVC. This study involved 57 patients who clearly fulfilled task force criteria and 59 patients who fulfilled some but not a sufficient set of criteria for ARVC. In the group with documented ARVC, mutations were found in 1 or more desmosomal protein genes in 51% of patients. PKP2 mutations were more common than mutations in DSG2 or DSC2. Biallelic and digenic mutations were also identified in this group. In contrast, when the diagnosis was not so firmly established, mutations were identified in only a small minority of patients (<20%).

In many ways, these 2 studies are remarkably similar. When the diagnosis of ARVC is firmly established on the basis of objective criteria, the chance of identifying 1 or more desmosomal mutations is ~50%. PKP2 mutations seem to be most common, and it is usual to find >1 desmosomal protein gene mutation. When the diagnosis is less certain, the chances of finding a desmosomal mutation fall off considerably.

These observations add to the collective database of desmosomal mutations in patients with heart disease and further strengthen the conclusion that mutations in desmosomal genes cause ARVC (at least as defined by the international task force criteria). Because desmosomes are cell-cell adhesion junctions, it is plausible to suggest that loss of function may play a role in disease pathogenesis. This is almost certainly true. Although desmosomes occur in virtually all solid tissues, clinical manifestations of desmosomal mutations are seen only in the heart and skin, organs that experience the greatest mechanical stress as part of their normal function. However, we know virtually nothing about potential alterations in cellular biomechanics in cardiac myocytes harboring mutations in desmosomal genes, nor do we know how such alterations might promote cardiac myocyte injury. Recent advances have linked altered distribution of desmosomal proteins in mouse models of ARVC to abnormal nuclear signaling, which provides opportunities for elucidation of new disease pathways.8 But so many questions remain.

First, what about the roughly 50% of patients in whom the diagnosis of ARVC was firmly established on the basis of task force criteria but who were found in these 2 studies not to have mutations in desmosomal protein genes? What is the cause of their disease? Do they even have the same disease as those with desmosomal mutations? Other candidate genes have been identified as potential causes of ARVC, including those encoding the cardiac ryanodine receptor (RyR2), transforming growth factor-β (TGF-β), and transmembrane protein-43 (TMEM43). Of these, the firmest link between a mutation and the disease has probably been established for TMEM43.9 In the case of RyR2, it remains controversial as to whether the disease phenotype is truly ARVC or a variant of catecholaminergic polymorphic ventricular tachycardia. It is noteworthy that neither of the articles in this issue of Circulation Cardiovascular Genetics screened patients for mutations in these nondesmosomal genes. Even if they had, it seems unlikely that this would have accounted for a significant number of individuals with documented disease but no identifiable desmosomal mutation. Other mutations in as yet unidentified genes must play a significant role in causing ARVC. There may be nongenetic causes as well.

A second important question has to do with the emerging pattern of multiple mutations in ARVC. Several studies have now shown that mutations and/or sequence variants in PKP2 seem to be most frequently identified in patients with clinically documented ARVC.10,11 However, it is not clear that all or even most of these mutations are sufficient to cause disease. It remains a formal possibility that these patients may have additional mutations in nondesmosomal genes that could be critical in disease pathogenesis. Epigenetic factors may also play important roles. We simply do not know. In any event, it now seems no longer sufficient to only screen the 5 major desmosomal protein genes in any serious effort to elucidate the genetic cause of ARVC.

Finally, what about the clinical and genetic differences between individuals with clearly established ARVC and those in whom task force criteria are not fulfilled? Certainly, individuals who did not meet task force criteria seemed to have some type of heart disease, and they also had a lower frequency of desmosomal mutations. Does this mean that only some of them actually had ARVC or is there a broader spectrum of disease than we currently recognize in classically defined ARVC? Experienced clinicians are aware of occasional patients who exhibit “overlap conditions” in which features of ARVC, ion channelopathies, and other forms of cardiomyopathy may appear to be blended together in complex phenotypes. Genotype-phenotype relationships in ARVC and its potential myriad variants remain a subject of mystery. Thus, despite the laudable efforts of the North American and Dutch groups, their work reminds us that we have probably only begun to scratch the surface. Although increased knowledge of mutations in desmosomal protein genes in classical ARVC will undoubtedly yield future insights into basic mechanisms of disease pathogenesis, we must also look beyond the desmosome and think about other
potential mechanisms and genetic causes. The rewards for developing a deeper understanding of the molecular pathogenesis of ARVC and elucidating potential genetic modifiers that determine disease severity may be the identification of fundamental mechanisms and the recognition of new targets leading to more rational mechanism-based therapies to prevent arrhythmias that cause sudden death rather than defaulting to implantation of devices designed to stop a lethal arrhythmia once it has begun. This is a goal to which we all should aspire.

Disclosures
Dr Saffitz has a pending patent application for a new diagnostic test for ARVC.

References

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