EDITORIAL

Arrhythmogenic Right Ventricular Cardiomyopathy: A Paradigm of Overlapping Disorders

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Arrhythmogenic right ventricular cardiomyopathy (ARVC), characterized by electrical and structural dysfunction, is a potentially high-risk disease associated with heart failure and sudden death, particularly in athletic individuals. Until recently, ARVC has been defined as a primary right ventricular disease characterized by fibrofatty replacement of the right ventricular myocardium associated with dilation and dysfunction of the right ventricle (RV) and, in some patients, RV aneurysm, and ventricular arrhythmias with left bundle branch morphology.[1] In recent years, left ventricular (LV) involvement has been appreciated and appears to occur with substantial frequency. However, based on its predominant RV symptoms, this is the myocardial chamber that is the main focus of investigation and the major chamber of the heart considered when defining the disease using the so-called "McKenna criteria" for the diagnosis of ARVC.[2] However, the RV is difficult to study, even in the current era, and the remaining features may be nondiagnostic. Hence, the diagnosis is difficult using conventional studies.

Taking into account the fact that ARVC is commonly an inherited disorder with autosomal-dominant inheritance, identifying the genetic basis of disease has been a major goal of many research groups. We hypothesized that ARVC would have a "final common pathway" leading to the disease when disturbed, similar to our assertions of a "final common pathway" for other cardiomyopathies and arrhythmia disorders.[3,4] In the case of hypertrophic cardiomyopathy, the "final common pathway" appears to be disruption of sarcomere function while dilated cardiomyopathy is a disturbance of sarcomere-sarcolemma linkage.[5] In the case of arrhythmia disorders such as Long QT syndrome (LQTS) and Brugada syndrome, defective ion-channel function leads to the classic clinical phenotype. In the case of ARVC, the genes identified to date encode proteins of the desmosome or desmosome-interacting proteins.[6–8] Based on disruption of this "final common pathway," the desmosome, in addition to other factors such as mechanical force, the disease develops over time, typically becoming clinically apparent in young adulthood. The right ventricle appears to become affected initially, ventricular arrhythmias develop before or after the development of overt RV disease, and the LV also becomes affected, usually later in the clinical course. The characteristic histopathologic features are commonly seen on myocardial specimens from transcatheter biopsy, explant associated with cardiac transplant, or autopsy. Animal models in which mutant desmosomal genes are engineered, commonly demonstrate separation of intercalated disks and loss of desmosomal proteins, and otherwise partially recapitulate the human phenotype.[8]

Despite the onslaught of all this new information, a firm mechanistic understanding of how the clinical phenotype develops has been elusive.[6–8] Is the clinical phenotype giving us a hint about the specific mechanisms or are these findings simply common responses to a scarred and fatty myocardium. One possibility to consider is that the mechanism of disease is a combination of disrupted overlapping pathways, resulting in a classic overlapping syndrome. This new mechanistic paradigm could work as follows: the genetic defect(s) that disrupt the function of the encoded desmosomal protein is, in and of itself, not sufficient to result in a structural or physiologic abnormality. Hence, the inherited genetic mutation simply provides a risk,

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from birth, of ultimately developing a clinical cardiac abnormality. Clinical development of the features of ARVC requires years of mechanical stress on the defective desmosomal protein and its weakened ability to bind its natural protein binding partners, leading to structural weakness of the desmosome and intercalated disk. This risk is amplified in athletes due to the increased mechanical force and stressors. Due to the geometry and structural strength of the RV, disruption of a critical mass of cell-cell contacts leads to early-onset RV dilation (and in some cases aneurysm formation) and dysfunction; the LV, however, is "protected" due to its geometry and strength generated from being a high-pressure chamber with a certain level of favorable hypertrophy. Over time, however, a critical mass of cell-cell contacts is disturbed and this "protection" is lost.

What about the arrhythmogenic features of ARVC? Again, the final common pathway hypothesis can be considered. As noted previously, the disturbed pathway in the case of rhythm disorders is ion-channel dysfunction. Ion channels and channel interacting proteins (ChIPs) are commonly found in the cardiomyocyte sarcolemma and may also be found in and around the intercalated disk.[9–11] One strong possibility that should be considered is that ion-channel function is disrupted via a "domino effect" situation in which desmosomal destruction leads to either disturbance of the normal binding of the affected desmosomal proteins with channels or alteration in ChIPs that are normal binding partners, and that this type of change can lead to the inability of the channel to function properly. Another possible scenario is that the desmosomal and intercalated disk abnormality disturbs the environment of the channels and ChIPs interacting with the intercalated disk, and this disturbance is enough to result in defective channel function. Both of these situations would predispose to channel dysfunction and the potential for a triggered arrhythmia. This is supported by the mechanisms causing LQTS where mutations in channel-encoding genes such as KCNQ1 (LQT1), KCNH2 (LQT2), or SCN5A (LQT3) lead to LQTS, in addition to the ChIP-encoding genes (ankyrin-B, caveolin-3, α1-syntrophin) that lead to LQTS. In the latter case, the clinical phenotype develops due to the interaction of the mutated protein with its binding partner (such as SCN5A), resulting in channel dysfunction and clinical mimicry of an LQT3-like picture.[10,11]

Could arrhythmias occur due to fibrosis and fatty infiltrate leading to an "irritable focus" and degenerate into a triggered arrhythmia? Certainly, this is the "conventional wisdom" and is feasible but specific data for this are somewhat limited. New knowledge occasionally requires consideration of a new mechanistic paradigm to explain the disease in question. Since these patients remain at moderate risk and therapy is limited to placement of an internal cardioverter defibrillator (ICD) and medications such as sotolol, a novel mechanistic understanding of the at-risk targets may lead to the development of new (and potentially better) targeted strategies in the care of these affected individuals. We have seen this, for instance, in dilated cardiomyopathy where inotropic therapy, once hailed as the therapy of choice, has fallen to the wayside in favor of β-blocker therapy, a negative inotrope. In non-cardiac disorders such as peptic ulcers, the once clear-cut mechanism of disease and therapies of the day have been replaced by newer thinking and new treatment options. Clearly, data will be the way to answer this conundrum.

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