Expanding the Spectrum of Arrhythmogenic Cardiomyopathy*

Jeffrey E. Saffitz, MD, PhD, FACC
Boston, Massachusetts

Of the nonischemic (familial) cardiomyopathies, only arrhythmogenic right ventricular cardiomyopathy (ARVC) specifies a particular cardiac chamber in its name. This is not surprising in view of the striking right ventricular (RV) involvement in the classical form of the disease, which is defined by relatively specific but not highly sensitive clinical criteria (the International Task Force criteria) (1) and/or pathological features of replacement of RV free wall myocardium by fat and fibrous tissue and aneurysms of the RV apex, posterior free wall, and outflow tract (the so-called “triangle of dysplasia”) (2). For many years after ARVC was first described clinically and pathologically, attention was understandably focused on the RV, and it was generally held that the left ventricle (LV) was normal or only minimally involved. In recent years, however, LV involvement has been recognized (3) and, in some cases, the LV might be the primary chamber to show pathological changes classically seen in the RV form. But the most important development in this field has been the crescendo of discovery about the genetic basis of ARVC (and its LV variants) and the recognition that most disease-causing mutations involve genes encoding proteins of the desmosome (4).

See page 2175

To date, mutations have been identified in virtually all desmosomal proteins, including the desmosomal cadherins (desmoglein-2 and desmocollin-2) and intracellular linker proteins of the plakin and armadillo families including desmoplakin, plakoglobin, and plakophilin-2. And now, in a paradigm shift away from conventional clinicopathological ascertainment of disease, it is the genetics that are beginning to drive the discovery of a far broader spectrum of disease phenotypes than originally appreciated in previous years.

In this issue of the Journal, the highly productive Inherited Cardiovascular Disease Group led by William J. McKenna at the Heart Hospital in London describes the clinical-genetic profile of 42 patients with a disease entity they term “left-dominant arrhythmogenic cardiomyopathy” (LDAC) in a report that significantly broadens the boundaries of arrhythmogenic cardiomyopathy (5). They defined LDAC as showing “early and predominant LV involvement” manifest clinically as inverted T waves in the lateral and/or inferior leads and ventricular arrhythmias of right bundle branch block morphology consistent with LV origin. They also included some patients with idiopathic myocardial fibrosis (IMF), a poorly defined entity that apparently accounts for a few percent of sudden cardiac deaths and is characterized pathologically by interstitial fibrosis, especially of the inferior LV wall, in the absence of coronary artery disease or other structural abnormalities. The rationale for including IMF in the spectrum of arrhythmogenic cardiomyopathy was both clinical and genetic—the clinical profile of IMF seems to overlap with LDAC, and a desmoplakin mutation was identified in a family with clinical features of ARVC who had lost a first-degree relative to IMF. Many of the LDAC patients presented with symptoms of arrhythmias or chest pain but not heart failure, thus distinguishing LDAC from other nonischemic cardiomyopathies such as dilated cardiomyopathy in which arrhythmias typically occur in the setting of ventricular dysfunction. Indeed, a defining feature of LDAC is arrhythmogenesis “out of proportion to the degree of ventricular dysfunction” (5).

McKenna et al. (5) also stressed that the types of ECG findings seen in many of their patients are often dismissed as benign in the absence of coronary artery obstruction or LV systolic dysfunction.

The LDAC patients in this study either had a proven family history of LDAC/IMF or were selected from a larger study population who were referred primarily for “difficult-to-manage arrhythmia or challenging risk stratification issues” in the setting of presumed dilated cardiomyopathy, hypertrophic cardiomyopathy, mitral prolapse, or myocarditis/LV noncompaction. In many cases, the original diagnoses were ruled out, indicating that LDAC is often unrecognized or misdiagnosed.

Genetic analysis identified disease-causing mutations in 7 of 24 families (13 of 34 individuals) with LDAC/IMF, a “pick-up” rate of 29%, which is roughly equivalent to that reported for classical ARVC (4). Five of the 7 mutations occurred within the gene encoding desmoplakin, perhaps suggesting that desmoplakin mutations are more likely than other desmosomal gene mutations to affect the LV. Of course, additional studies will be required to validate this potential relationship. It is clear, however, that much remains to be discovered about the genetic basis of arrhythmogenic cardiomyopathy, and it can be anticipated that mutations in genes other than those encoding desmosomal proteins will eventually be identified. Interestingly, all 4 LDAC patients who originally presented with chest pain and were presumed to have viral myocarditis were found to...
have desmosomal mutations. This observation lends credence to the notion that inflammatory myocarditis in the setting of arrhythmogenic cardiomyopathy has a genetic rather than an infectious etiology.

Five study patients fulfilled echocardiographic criteria for LV noncompaction. Of these, 2 showed fibrofatty replacement on endomyocardial biopsy and carried desmosomal gene mutations. One had a family history of pathologically documented ARVC, and another died suddenly and was found to have a post-mortem picture of IMF (but not LV noncompaction). The final patient was Afro-Caribbean, a population in which at least some normal individuals fulfill criteria for noncompaction. These observations provide additional links between noncompaction and the spectrum of arrhythmogenic cardiomyopathy while also emphasizing that current diagnostic criteria for LV noncompaction require further refinement.

Cardiac magnetic resonance imaging revealed segmental dilation and/or wall motion abnormalities in the RV in a majority of LDAC patients. Right ventricular aneurysms were present in roughly one-third, and diminished RV ejection fraction was observed in roughly one-quarter of LDAC patients. This raises questions about whether some patients had the “biventricular” form of arrhythmogenic cardiomyopathy (defined as early and parallel involvement of both ventricles) rather than the left-dominant form in which the LV is primarily affected. In any event, it is becoming increasingly apparent that there might be a continuum of disease phenotypes in arrhythmogenic cardiomyopathy from classical ARVC to the biventricular form to LDAC in which features of IMF and ventricular noncompaction might also be manifest.

Increased recognition of the range of disease phenotypes necessitates a change in nomenclature. Under any circumstances, the term “dysplasia” is entirely inappropriate in describing the pathological changes seen in ARVC and the biventricular and left-dominant variants. Dysplasia implies an abnormality of proliferative growth, and the fact that mature cardiac myocytes are post-mitotic automatically precludes the use of this term. New insights into molecular mechanisms suggest that cardiac myocytes undergo degenerative changes in response to a primary myocyte disease process, eventually leading to cell death and replacement by a fibrofatty type of scar tissue. Although suitable for the classical form of disease, ARVC is obviously not appropriate for the broader spectrum of diseases characterized by the common features of arrhythmias out of proportion to ventricular dysfunction, fibrofatty replacement of myocardium, noninfectious inflammatory infiltrates, and mutations in desmosomal (and as yet undiscovered) genes regardless of ventricular predominance. As used in this commentary, the term “arrhythmogenic cardiomyopathy” with right-dominant, biventricular, and left-dominant subtypes has been applied increasingly and is appropriately focused on the primary importance of arrhythmias as an early feature of disease. While some might object to this term by pointing out that arrhythmias are a common feature of many types of cardiomyopathies, the unusually high incidence of arrhythmias in the absence of significant ventricular remodeling and dysfunction justifies adoption of this nomenclature. More detailed understanding of potential mechanistic links between arrhythmogenic cardiomyopathy and other entities such as IMF and ventricular noncompaction will require further analysis. Major advances can certainly be anticipated as the genetic basis of arrhythmogenic cardiomyopathy becomes more completely understood.

Reprint requests and correspondence: Dr. Jeffrey E. Saffitz, Department of Pathology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215. E-mail: jsaffitz@bidmc.harvard.edu.

REFERENCES


Key Words: arrhythmia • cardiomyopathy • genetics • magnetic resonance imaging • sudden death.