Editorial

Reconciling the Protean Manifestations of Arrhythmogenic Cardiomyopathy

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Medical conception of a disease begins with in vivo observation and develops with recognition of cognate findings on gross anatomy, histology, and cellular pathology. It was histopathology that established myocyte disarray as the cardinal feature of hypertrophic cardiomyopathy, present even in cases where left ventricular (LV) hypertrophy is subtle or absent. To this day, clinical-pathological association retains its historical value as the primary means of gaining insight into underlying disease processes. Enhancing its appeal is its accessibility to physicians, most of whom are familiar with histopathology from medical school and attuned to visual diagnosis.

With the advent of molecular genetics, however, the limitations of clinical-pathological association have become apparent and nowhere more so than in the inherited arrhythmia syndromes. In the long-QT and Brugada syndromes and catecholaminergic polymorphic ventricular tachycardia, a structurally normal heart belies the propensity to ventricular arrhythmia and sudden cardiac death (SCD). How this might be possible began to unravel with the isolation of mutations in genes encoding ion channels, transporters, and binding proteins. Genetic studies also have provided fresh insights into diseases with an obvious pathological substrate, such as hypertrophic cardiomyopathy, in which sarcomeric mutations predominate. Families with a high incidence of SCD and myocyte disarray but minimal LV hypertrophy were found to have mutations in troponin T, lending further support to the inclusion of this phenotype within the spectrum of hypertrophic cardiomyopathy.

Redefining diseases according to their genetic etiology, while attractive, is less straightforward than immediately obvious. Defects in sarcomeric components, for example, have been implicated in both hypertrophic cardiomyopathy and dilated cardiomyopathy. In some heritable disorders, such as dilated cardiomyopathy, marked locus heterogeneity precludes delineation of a single genetic determinant. The ultimate solution to disease classification involves going 1 step further and identifying a unifying molecular mechanism, which may afford the added benefit of novel therapeutic targets. The so-called final common pathway in dilated cardiomyopathy may be compromised linkage of sarcomere to sarcolemma through the cytoskeleton. Hypertrophic cardiomyopathy purportedly results from myocardial energy depletion, providing a rational basis for treatment success with perhexiline.2

In contrast, attempts to define arrhythmogenic cardiomyopathy appear to have come full circle. The histological substrate in arrhythmogenic cardiomyopathy ranges from purely fibrotic in Carvajal syndrome to predominant adipose replacement and may be absent altogether in early disease, precluding characterization on pathological grounds alone. An estimated 30% to 60% of cases harbor variants in desmosomal genes (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2, and desmocollin-2). Definition on this basis, however, is deterred by the recent isolation of causal variants in extradesmosomal genes. Transmembrane protein 43 (TMEM43), the function of which is still being elucidated, has been implicated in arrhythmogenic cardiomyopathy in the Newfoundland founder population. The spontaneous syndromic form of arrhythmogenic cardiomyopathy in Poll-Herford cattle has been linked with a defect in nuclear factor-κB interacting protein 1, which interacts with a family of transcription factors regulating genetic control of inflammation, cell proliferation, and survival.3

Putative disease mechanisms for arrhythmogenic cardiomyopathy nonetheless invoke a final common pathway of desmosomal dysfunction. The symmetrical desmosomal complex bridges the space between adjacent cells and tethers intermediate filaments to the cell surface at either end. Components of the desmosome also can translocate between subcellular compartments and participate in signal transduction. Desmosomal protein defects may impair intercellular adhesion, intermediate filament function, or both, thereby reducing resilience to mechanical stress and pressure, also perturb intracellular signaling pathways. In animal and in vitro models, cardiac-specific suppression of desmoplakin leads to nuclear translocation of plakoglobin and inhibition of canonical Wnt/β-catenin signaling, with transcriptional modulation of genes involved in cell proliferation and differentiation. Among the overexpressed targets are the collagens, which contribute to fibrosis, and bone morphogenetic protein 7, Wnt5b, and peroxisome proliferator-activated receptor γ, which promote adiposis, recapitulating the histopathologic substrate of arrhythmogenic cardiomyopathy. Of note, the
extradesmosomal disease gene **TMEM43** contains a response element for peroxisome proliferator-activated receptor \( \gamma \).3, 4

A recently described immunohistochemical assay exploits the translocation of plakoglobin as a key molecular event in arrhythmogenic cardiomyopathy. In a pilot series, myocardial samples from 11 subjects with arrhythmogenic cardiomyopathy demonstrated significant reduction in the immunoreactive signal level for plakoglobin at intercalated disks.5 There was a false-negative finding in an individual fulfilling clinical criteria for arrhythmogenic cardiomyopathy, raising questions about the sensitivity of diminished plakoglobin signal for early disease. A case of cardiac sarcoidosis resulted in a false-positive, underscoring the need for further work to elucidate the shared signaling and inflammatory pathway.5 The molecular underpinning of arrhythmogenic cardiomyopathy undoubtedly is complex; the heterogeneity of known disease loci points to additional players and pathways still to be elucidated. At present, a unifying paradigm for arrhythmogenic cardiomyopathy remains elusive and classification on the basis of mechanism premature.

Process of elimination leaves the default option of a clinical definition for arrhythmogenic cardiomyopathy, although this too poses significant challenges. Prior designations have emphasized the right ventricular (RV) preponderance of the disease in its classic form. Depending on the selection criteria for the cohort and the evaluation protocol used, however, the prevalence of LV involvement is estimated at 15% to 93%; the principal distinction between the disease pattern is in its timing and relative prominence. LV involvement is a late complication of classic disease, arising after the onset of global RV dysfunction but occurs early in the other subtypes, either in parallel with or predominating over RV disease. The biventricular and left-dominant subtypes are part of the expression of desmosomal disease, and all three patterns may coexist within families.6, 7

The most inclusive definition currently available for arrhythmogenic cardiomyopathy is based on its natural history. Arrhythmogenic cardiomyopathy is a heritable disorder characterized by an early propensity to ventricular arrhythmia that is disproportionate to the extent of morphological dysfunc-

tion, with subsequent development of progressive myocardial disease. In its early stages, arrhythmogenic cardiomyopathy belongs with the inherited arrhythmia syndromes and, in its latter stages, the cardiomyopathies.1a Intrinsic to this definition is the distinction of left-dominant and biventricular arrhythmogenic cardiomyopathy from dilated cardiomyopathy. Dilated cardiomyopathy typically presents with heart failure and arrhythmogenic cardiomyopathy, as its name implies, with ventricular arrhythmia (or, less commonly, a myocarditis-like episode). In dilated cardiomyopathy, LV systolic dysfunction is a key predictor of arrhythmic events; in arrhythmogenic cardiomyopathy, the arrhythmic risk may be significant despite preserved ventricular function.7

An immediate drawback of this description, however, is its failure to intellectually satisfy physicians, owing to our preference for envisioning diseases with a structural or histological signature. A more pragmatic caveat is the need to elicit a detailed clinical history from the individual and any available relatives to determine the disease pattern, which compounds the existing diagnostic difficulty in arrhythmogenic cardiomyopathy. As yet, there is no gold standard test for arrhythmogenic cardiomyopathy because its clinical manifestations are protein and nonspecific. Any affected individual will demonstrate but a few of the broad range of electrocardiographic, arrhythmic, and structural abnormali-
ties. The features with the most discriminatory power, based on receiver operating characteristic curves, have been incorporated into the Task Force criteria, which facilitate diagnosis of classic right-dominant arrhythmogenic cardiomyopathy.8 Pilot guidelines also have been proposed for diagnosis of nonclassic subtypes.7 Yet, an unresolved issue is how these diverse clinical features relate to the underlying disease process.

The primary tool for addressing this question remains clinical-pathological association, which has provided invaluable insight into the natural history and phenotypic spectrum of arrhythmogenic cardiomyopathy. Examination of ex vivo hearts offers the unique advantage of access to extensive histology but also has its limitations. SCD is the first clinical manifestation of arrhythmogenic cardiomyopathy in 23% to 50% of index cases, resulting in a paucity of available clinical data to complement pathological observations. The inevitable focus on individuals with SCD and transplant recipients also provides a skewed perspective of a disease that, in a significant proportion of subjects, is associated with favorable outcomes.3, 6

An alternative strategy involves the use of in vivo imaging as a surrogate for pathological examination. In this capacity, cardiovascular magnetic resonance (CMR) may have the edge. Besides quantifying ventricular volumes and function, CMR enables gross tissue characterization with T1-weighted fast-spin echo sequences (for fat) and late gadolinium enhancement (LGE) imaging (for fibrosis or fibroadiposis).9 There are several reported associations between CMR findings and ECG abnormalities. Right precordial QRS prolongation, for example, is associated with higher RV end-diastolic volumes and RV-to-LV volume ratio, reduced RV ejection fraction, and a greater extent of LGE/fatty replacement of the RV myocardium.6 Similar associations with RV imaging indices have been reported for late potentials.9, 10 Ventricular arrhythmia originating from a particular focus commonly coincides with localized dilation, wall motion abnormality, or LGE at the same site on CMR.6 Although imaging cannot provide histological data, this disadvantage is partly offset by the broader available case mix, representing the full spectrum of disease from mild to severe.

In this issue of *Circulation: Arrhythmia and Electrophysiology*, Santangeli et al11 describe the adoption of a novel approach to the investigation of substrate/clinical feature associations. Substrate in their study is represented by low-voltage areas (LVA) on electroanatomic mapping. All 17 cases satisfied task force guidelines and had biopsy evidence of arrhythmogenic cardiomyopathy in accordance with accepted histopathologic criteria. Implicit in this methodology is the assumption that LVA are a corollary of myocyte loss with fibrofatty replacement, which is justifiable in the context of the biopsy data.11 A number of the associations identified warrant further discussion.
First, the 8 (47%) cases with contributory abnormalities on 12-lead ECG had a higher number of LVA in the RV than the remainder. The major inference is that the presence of ECG abnormalities is an indicator of the extent of underlying substrate. Perhaps less expected, but also noteworthy, is the absence of surface ECG abnormalities in more than one half of the study sample in whom the disease was detectably less diffuse. That a normal ECG does not exclude arrhythmogenic cardiomyopathy is well established, albeit not widely appreciated. Among a prior reported series of 132 affected relatives, the prevalence of ECG abnormalities was coincidentally identical at 47%. Limited phenotypic expression is common among presymptomatic family members ascertained through prospective evaluation. In the present study, however, a family history of arrhythmogenic cardiomyopathy was elicited in only 4 (24%) cases. Ventricular arrhythmia, on the other hand, was a universal finding, taking the form of nonsustained ventricular tachycardia in 41% and frequent (>1000 per 24 hours) ventricular extrasystoles in 59%. What is conspicuous is the low frequency of ECG findings among individuals with notable ventricular arrhythmia. The implication is that a normal 12-lead ECG not only is compatible with arrhythmogenic cardiomyopathy, but also may belie significant arrhythmic risk.

Second, late potentials on the signal-averaged ECG were associated with LVA in the RV outflow tract. Furthermore, component signal-averaged ECG parameters showed significant positive correlation with the mean bipolar electrogram voltage amplitude in the outflow tract. Although the pathological underpinning of late potentials in arrhythmogenic cardiomyopathy has received attention in the past, the link with RV outflow tract involvement appears novel. From a clinical standpoint, the finding of late potentials should prompt careful imaging and electrophysiological interrogation of the RV outflow tract. This recommendation is unlikely to change practice per se because the RV outflow tract warrants careful examination in any work-up for suspected arrhythmogenic cardiomyopathy, as do the subtricuspid region and apex as components of the “triangle of dysplasia.”

The association may be of particular relevance, however, in the differentiation of idiopathic RV outflow tract tachycardia from arrhythmogenic cardiomyopathy, which continues to pose a major clinical challenge. The dilemma is magnified by the perception that right precordial T-wave inversion, one of the main ECG markers of arrhythmogenic cardiomyopathy, also might arise from cardiac memory of repolarization during ventricular ectopic activity. The diagnostic contribution of a positive signal-averaged ECG may likewise be queried in light of the 5% prevalence of late potentials in the ostensibly healthy general population. The findings of Santangeli et al argue against devaluing the signal-averaged ECG in the setting of RV outflow tract tachycardia. Unfortunately, a normal signal-averaged ECG does not exclude underlying cardiomyopathy. Electroanatomic mapping itself may be of value, with LVA identifying subjects with fibrofatty myocardial replacement on biopsy and increased incidence of recurrent ventricular arrhythmia following successful ablation. RV outflow tract tachycardia may, however, be the sole initial finding in arrhythmogenic cardiomyopathy, mandating continued follow-up and reassessment to avert representation with an arrhythmic event.

Third, the distribution of LVA showed significant concordance with RV LGE and, to a lesser extent, with regional RV dysfuncion. In a prior report on the diagnostic role of CMR, RV wall motion abnormalities, when mild, were highly sensitive for arrhythmogenic cardiomyopathy and, when severe, were highly specific. That abnormal wall motion on imaging corresponds to underlying substrate has been more difficult to demonstrate but is supported by the present study. Individuals with RV LGE have been previously shown to have fibrofatty changes on endomyocardial biopsy samples from the interventricular septum. Coincidence of LGE segments with LVA on electroanatomic mapping and biopsy specimens obtained from these sites provides the strongest indication to date of an association with histological substrate.

Does the weight of evidence now favor inclusion of RV LGE in forthcoming revisions of the Task Force criteria? Perhaps, but demonstration of this feature requires experienced operators and readers, for right-sided LGE is as prone to misinterpretation as electroanatomic mapping itself, unless in expert hands. The interobserver reproducibility of RV LGE awaits systematic investigation. The major difficulties stem from the thinness of the RV wall and the need to distinguish normal epicardial fat from myocardial LGE. The sequence parameters and setup used for standard LGE imaging of the LV must be optimized accordingly. Some authors have suggested, for example, that nulling of the RV myocardium requires shorter inversion times than the left; others, however, contest that this is artifactual and that achieving sufficient spatial resolution is key, potentially through acquisition of systolic slices. Chemical-shift fat suppression and use of the body coil instead of the cardiac surface coil also may reduce noise and improve discrimination, but the techniques remain largely the remit of specialist centers.

Most CMR operators and readers are, however, skilled in acquisition and interpretation of left-sided LGE images. There may in fact be a stronger case for incorporation of LV LGE among the imaging criteria for arrhythmogenic cardiomyopathy. LV LGE is the most common CMR abnormality in left-dominant arrhythmogenic cardiomyopathy where it frequently occurs without coincident regional or global LV dysfunction and is associated with interstitial or reparative fibrosis on histopathology. In the classic, right-dominant subtype, both LGE and tagging appear to be sensitive indicators of LV involvement, which is a marker of late-stage disease and adverse prognosis. Tagging enables quantification of early LV segmental dysfunction, while LGE may be an aid to diagnosis. In arrhythmogenic cardiomyopathy, LV LGE occurs in a subepicardial or midwall pattern, mirroring the distribution of fibrofatty substrate on histopathology and facilitating differentiation from the subendocardial involvement of ischemic scarring.

Although CMR is a powerful and indispensable technique for delineating anatomy in arrhythmogenic cardiomyopathy, emerging evidence suggests that electroanatomic mapping might prove superior in early disease. Santangeli et al allude to this as they highlight the limited sensitivity of RV LGE, which was present in only 8 (62%) of 13 cases with
LVA on electroanatomic mapping. This finding is consistent with the reported 59% sensitivity of RV LGE for genetically proven disease in an earlier study. Electrophysiologists may argue that voltage mapping provides 3D reconstructions with high spatial resolution, but the disparity in performance may have less to do with the relative merits of the techniques than with the nature of the disease itself.

The arrhythmic substrate in “concealed” arrhythmogenic cardiomyopathy almost certainly differs from the fibrofatty atrophy of overt disease. Myocyte necrosis accompanied by an inflammatory response was the primary molecular event in mice overexpressing the N271S-dsg2 mutation. Similar myocar dic changes are present in up to 79% of postmortem hearts with arrhythmogenic cardiomyopathy and represent a potential substrate for arrhythmia; CMR, however, has the capacity to detect this, through short-τ inversion-recovery sequences, for example. Heterozygous plakoglobin-deficient mice developed spontaneous ventricular ectopy in the absence of histological changes, but this was accompanied by increased RV volumes and reduced ejection fractions, which again would be discernible by imaging.

The limitations of imaging become apparent in the case of a 5-year-old girl who was homozygous for the plakoglobin deletion of Naxos disease. Her 12-lead ECG demonstrated right precordial QRS prolongation, epsilon waves, and deep inverted T-waves, although the latter may have been attributable to a normal juvenile pattern. Patently abnormal were the results of 24-hour Holter monitoring, which showed in excess of 14 000 ventricular extrasystoles of predominantly RV origin. At the age of 7, she died from a cerebral hemorrhage, a likely complication of the hematologic malignancy she had been battling for 2 years. Postmortem examination of her heart conspicuously failed to identify any myocyte necrosis, fibrofatty changes, leukemic infiltrates, or signs of chemotherapy-related injury. Electron microscopy and immunohistochemistry revealed a reduction in the number and size of gap junctions and diminished expression of connexin 43 at intercalated disks. Desmosomal dysfunction may result in gap junction remodeling, which in turn gives rise to heterogeneity of electric conduction in the ventricle, providing the substrate for arrhythmia and manifesting as depolarization abnormalities on the 12-lead ECG. Similar abnormalities of connexin 43 expression have since been identified in autosomal-dominant arrhythmogenic cardiomyopathy.

Could electroanatomic mapping detect early conduction heterogeneity consequent to gap junction remodeling before the development of a histological substrate? Answering this question will require invasive mapping studies of individuals with a proven disease-related genotype (genetic complexity notwithstanding) and normal imaging. The combination of LVA, negative histological biopsy specimens, and abnormal gap junctions would establish a role for electroanatomic mapping in the early diagnosis of arrhythmogenic cardiomyopathy. At present, arrhythmogenic cardiomyopathy retains the unique profile of a disease in which clinical manifestations arise from different mechanisms at different stages of its natural history (Figure).

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Disclosures
None.

References
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