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Viewpoint

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Disputation on the power and efficacy of phenotypical classification in arrhythmogenic cardiomyopathy: Time for a reformation?!

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Representing the spark that lit the Protestant Reformation, on the 31st of October Anno Domini 1517 Reverend Martin Luther sent the manuscript entitled "*Disputation on the Power and Efficacy of Indulgences*" to the Archbishop of Mainz for academic disputation or, as it would be called today, external peer review. This document challenged well-established religious beliefs of the time, leading to massive changes across a society ripe for transformation yet deeply entrenched in outdated beliefs.

Similar to 16th century Europe, in the last 4 decades, research on arrhythmogenic cardiomyopathy (ACM) has been heavily anchored to a phenotype-based framework. In light of piling evidence, however, such an approach may now appear outdated. Much like *Luther*, we believe a change in perspective is necessary. Our goal is to describe the evolution of phenotypical classification from right ventricular dysplasia to ACM and its challenges, and to provide the rationale for a new paradigm. The new ACM model would be *centered on* the individual's genetic underpinnings and *informed* with phenotype, with the potential to advance precision care and enable systematic research efforts.

The problem of phenotypical classification in ACM

Currently, cardiomyopathy diagnoses rely on distinct phenotypical features.[1] Acronyms and definitions of ACM have varied widely over the years, with much confusion for clinicians, researchers, and patients. As the name suggests, the defining feature of ACM is agreed to be the increased risk of ventricular arrhythmias in a nondilated, nonhypertrophic, nonischemic structural heart disease. However, because phenotype lies in the eyes of the beholder, the spectrum of phenotypes referred to as "ACM" evolved over time. Nearly 2 centuries after its initial report by Giovanni Maria Lancisi in the 18th century, right ventricular dysplasia was first described as a distinct clinical entity by Marcus et al[2] in 1982. To systematically capture this particular phenotypical trait, the Task Force Criteria (TFC) were introduced in 1994 and revised in 2010 incorporating additional diagnostic modalities and genetic testing.[3,4] In the past decade, however, an increased number of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) genotypes presenting with early and disproportionate left ventricular involvement has been reported. Per the nominative determinism that permeates the cardiology community, these forms have been referred to as arrhythmogenic left ventricular cardiomyopathy (ALVC). In 2019, the Heart Rhythm Society Consensus Statement introduced the controversial term "ACM" as an umbrella definition, including noninheritable cardiac diseases, expanding the list of ACM forms beyond genetic and exercise-induced forms.[5] Almost at the same time, the term "ACM" was used in the Padua Criteria, which represent the first attempt at updating the diagnostic criteria to capture both ARVC and ALVC phenotypes.[6] These documents have fostered a divergence in the perspectives of many North American and European clinicians regarding the defining characteristics of ACM.

As a result, ACM is often used to describe a vast spectrum of genetic and acquired phenotypes, including cardiac sarcoidosis, chagas cardiomyopathy, and myocarditis, in addition to typical ARVC and ALVC, particularly in some North America centers. Although these conditions seem to share certain phenotypical features, the vast differences in etiology, natural history, and phenotype profile preclude development of

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effective management strategies. The risk of using a single common phenotype definition (whichever it may be) for such a broad spectrum of diseases is the progressive regression of the phenotypical definitions toward the "average" ACM patient (if any such patient even exists). This regression to the mean created some fictitious sense of structure in this domain at the cost of a significant loss of valuable information, appearing deficient in the modern era of precision medicine.

The case for a genotype-based integrated diagnostic approach

Pathogenic (P) or likely pathogenic (LP) variants in multiple genes have been associated with different forms of ACM, with approximately two-thirds of patients fulfilling 2010 TFC phenotypes harboring such variants in ARVC-associated genes. Both the 2010 TFC and the Padua Criteria consider the presence of a P/LP variant a major diagnostic criterion.[4,6]

The possibility that diseases arising from different genes may share a similar, predetermined phenotype, however, does not imply they share etiology or natural history. Indeed, recent studies focusing on genotype in ACM have extensively challenged such a notion. Protonotarios et al[7] showed that even among patients fulfilling a 2010 TFC phenotype for ARVC, the reliability of arrhythmic risk assessment varied extensively depending on the underlying genotype. Paldino et al[8] went further, reporting the superiority of a genotype-based approach over a phenotype-based classification in ACM and dilated cardiomyopathy (DCM). Finally, the same P/LP variants in ACM-associated genes, such as desmoplakin (*DSP*) and phospholamban (*PLN*), were associated with various phenotypes, ranging from DCM to ARVC and ALVC.[9,10] The arrhythmic outcomes of patients with variants in the same genes were constantly elevated, independent of phenotype,[8] suggesting a stronger role for underlying genotype over phenotype. This evidence shows that not all genomic/molecular pathways leading to overlapping phenotypical expression share natural history or outcomes. However, under the current framework, patients with a *DSP*-associated and a plakophilin-2 (*PKP2*)-associated ARVC fulfilling the 2010 TFC would undergo the same diagnostic workflow, risk stratification strategy, and management. This seems irrational, as genotype has been consistently shown to represent a better determinant of arrhythmic outcomes–conceptually the only true gold standard to validate the diagnostic scheme for ACM, as the term implies.

Thus, a unified definition of ACM seems a flawed thought exercise. However, we do not imply that the phenotypical classification of ACM is of no value, as phenotype is frequently (especially in probands) the first hint of disease and does influence outcomes strongly in most cardiomyopathies. Rather, we see the problem of the current phenotype-based framework in its detachment from genotype—arguably the strongest driver in natural history of disease. Most phenotypical predictors of outcomes in ACM are derived from the pregenomic era, with genotype-specific insights limited to the most common ARVC/ACM-associated genes, such as *PKP2*. Consequent to uniform diagnosis, the relative weight of the same risk factors, such as premature ventricular contraction (PVC) burden or exposure to physical exercise, is given a similar weight in ACM patients harboring either a *PKP2*-, *PLN*-, or *DSP* P/LP variant. Both the 2010 TFC and Padua criteria use the same PVC burden threshold as a diagnostic criterion for all these genetic forms. However, there are few data supporting these assumptions, whereas more substantial evidence supports genotype-based differences in the clinical significance of PVC burden.

Despite some recent gene-specific insights for certain genetic forms of ACM,[9,10] a systematic effort at genotype-first ACM characterization in clinical cohorts has not been attempted yet. Therefore, we envision a future in which ACM is categorized into subtypes through a nuanced consideration of genotype *and* phenotype (eg, *PKP2*-ARVC), and diagnostic and prognostic features will be gene-informed if not gene-specific. Adopting a genotype-based approach will ensure the consideration of the natural history of the disease in tandem with the clinical phenotype (ie, disease penetrance). Precisely defining the latter is the key impediment within a genotype-centered diagnostic framework. Consequently, such a paradigm shift necessitates an international and multidisciplinary effort to derive universally acceptable definitions of distinct genetic cardiomyopathy phenotypes, define genetic counseling indications to enable testing with a lower phenotype burden, and, most notably, facilitate the huge change of perspective and way of operations required. We consider such a gene-centered characterization of ACM subtypes to be a valuable and forward-looking endeavor, representing a long-awaited reformation in the ACM field.

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