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EDITORIAL COMMENT

Desmoplakin-Specific ARVC Risk Scores

Deep Phenotyping to Drive Precision Medicine*

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A case series in 1982 was the first detailed description of a disease pathology characterized by fibrofatty replacement of the right ventricular myocardium and a proclivity toward sudden cardiac death (SCD) in affected individuals.[1] Since this initial description, arrhythmogenic right ventricular dysplasia has held many monikers reflecting our growing understanding of this condition and its heterogenous phenotypes. Mounting evidence that the characteristic dysplastic tissue findings were progressive rather than congenital prompted a name change from dysplasia to cardiomyopathy (arrhythmogenic right ventricular cardiomyopathy [ARVC]). Imaging and tissue-level analysis have even led to the identification of inflammatory infiltrates, leading to the characterization of some ARVC as inflammatory cardiomyopathy.[2] More recently, identification of biventricular involvement and left predominant disease expanded the family of related conditions to include arrhythmogenic cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy, respectively.[3] This challenging nomenclature underscores the heterogeneity in ARVC that has thwarted efforts to predict SCD and highlights the need for ongoing precision medicine efforts such as the current study[4] to reassess (and eventually refine) risk calculators based on genotyping and deep phenotyping.

Indeed, incident SCD estimates from prospective ARVC cohorts have ranged widely from 3.27 to 10.02 deaths per 1,000 per year, with meta-analytic rates of aborted SCD or SCD as high as 20.72 per 1,000 per year for patients with definite ARVC by 2010 task force criteria (TFC).[5,6] More recently, a 2019 study identified clinical characteristics associated with incident sustained ventricular arrhythmia (VA) in a cohort of participants in whom the majority of pathogenic or likely pathogenic variants were plakophilin (PKP2).[7] Despite assembling an impressive international cohort of patients with TFC ARVC, the resultant calculator had uncertain external validity for risk prediction beyond the research cohort. There are at least 13 genes associated with ARVC, desmosomal and nondemosomal, in addition to genotype-negative ARVC, with differences in disease characteristics and prognosis.[8]

In the current study in this issue of *JACC: Advances*, Gasperetti et al[4] highlight how genotypic variation impacts risk prediction using meticulously curated multinational registry data to amalgamate the largest published cohort of patients with definite ARVC by TFC and pathogenic or likely pathogenic desmoplakin (DSP) variants. The authors should be commended on the rigorous application of their 2019 ARVC risk tool to this DSP population, demonstrating it is not an effective predictor of VA in this population, especially with disease involving the left ventricle. One might infer that differences in genotype—DSP vs largely PKP2 variant ARVC—are in part responsible for the lack of efficacy of this tool. The DSP cohort had a higher incidence of sustained ventricular tachycardia and PVC burden than the 2022 index cohort used to derive the calculator, suggesting that TFC-confirmed ARVC patients with DSP variants may have greater arrhythmia burden.[7] Moreover, male sex, an established risk factor for arrhythmia in ARVC, was not associated with the primary outcome of first-sustained VA in the current study.

Consistent with prior observations, DSP-variant cardiomyopathy has a predilection for left

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ventricular involvement, which makes DSP-variant ARVC fundamentally different from its PKP2-variant relative. There is insufficient data on whether similar risk estimates can be applied for individuals with left ventricular, right ventricular, or biventricular involvement. DSP-variant ARVC is clinically divergent enough that the TFC has a lower sensitivity for diagnosis of this condition. Thus, we can expect that many participants with arrhythmogenic potential were excluded from this cohort for not meeting TFC.[9] As Gasperetti et al show, future attempts to construct risk calculators might have higher accuracy by utilizing single gene variant cohorts to eliminate some of the heterogeneity that impacts predictive accuracy and, in doing so, provide valuable prognostic data for patients earlier in their disease course who may benefit from an implantable cardioverter-defibrillator.

The 2019 ARVC risk calculator utilizes nonsustained ventricular tachycardia (3 or more beats for >120 beats/min) for prediction of sustained ventricular tachycardia, but treating nonsustained ventricular tachycardia (NSVT) as a binary variable likely blunts its effectiveness as a risk factor. Prior work in hypertrophic cardiomyopathy indicates that NSVT that are fast (>200 beats/min), repetitive, and longer than 7 beats are more predictive of future appropriate implantable cardioverter-defibrillator shock than slow, single, and short events.[10] Deeper phenotyping of duration, rate, and characteristics of NSVT would likely improve risk stratification.

Use of spontaneous sustained VA >100 beats/min and lasting longer than 30 seconds as an endpoint is not an SCD equivalent, as the authors caution. Indeed, the original report on the first iteration of the ARVC risk score received some scrutiny and criticism for its high estimates of VA risk using this definition of sustained VA.[7] The investigators nimbly repeated their analysis (generating a second generation risk calculator) utilizing a higher-risk, "fast VA" endpoint (SCD, aborted SCD, ventricular fibrillation, or VT >250 beats/min).[11] It would have been interesting to see how this more rigorous definition of "fast VA" affects risk prediction of DSP patients in the present study. Future models should more deeply phenotype both the NSVT risk factor and the VA endpoint/outcome in developing genotype-specific risk calculators.

Finally, we address the issue of DSP-associated myocardial inflammation. Many ARVC variants, but particularly DSP have been associated with both chronic fluorodeoxyglucose-F18-avidity on positron emission tomography[12] as well as "hot phase" episodes of myocarditis-like injury heralding disease progression.[9,13] Early reports of diffuse lymphocyte infiltration into ARVC myocardium in up to two-thirds of patients and the presence of autoantibodies against intercalating disk components and myosin in some patients suggest that inflammation may play an important role in the pathogenesis of this disease.[2] Other work has identified a lack of correlation between fluorodeoxyglucose-F18-positron emission tomography scan positivity and endomyocardial biopsy results suggesting a component of myocardial metabolic derangement as well.[11] Deep phenotyping to determine inflammatory and metabolic components of DSP cardiomyopathy may improve future risk prediction models and calculators.

We eagerly await future studies from this impressive group of investigators, as their rigorous work helps us understand and counsel our most complex genetic cardiomyopathy patients. So what are some considerations for future ARVC risk models? 1) Genotypic variation may impact risk prediction despite broad inclusion in a single cardiomyopathy classification. 2) Not all VAs are the same, and careful deep phenotyping of both NSVT as a risk factor and VT as an endpoint/outcome may provide better risk estimates. 3) Understanding the association of myocardial inflammation and metabolism with clinical arrhythmia burden and risk will further efforts at precision medicine for these patients.

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