Challenges of Diagnosis and Risk Stratification in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia*

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a challenging clinical problem because it is relatively uncommon, a definitive diagnosis may be difficult in some patients, and the consequence of missing the diagnosis could be fatal. Moreover, the onset of symptoms occurs over a broad range of age. Worldwide registries and consensus documents have improved the criteria used to make the diagnosis and serve to disseminate information to physicians who do not see patients with this problem very often. The criteria are based on the results at referral centers compared with core laboratories (3).

The proposed guidelines for CMR criteria require the combination of severe regional wall motion abnormalities with global right ventricular dilation or dysfunction. Although these criteria maintain specificity, they may not have improved sensitivity for diagnosis (2). Moreover, interpretation of the results of diagnostic studies such as CMR is dependent on experience, and results from the North American Multidisciplinary Study have shown significant differences in the interpretation of diagnostic test results at referral centers compared with core laboratories (3).

The rate of progression of the disease has not been delineated, and with the advent of genetic testing, physicians are likely to be consulted about the management of asymptomatic carriers of desmosomal protein mutations, which is difficult to assess because of variable disease expression even within the same family (4). There is some evidence that electrophysiological abnormalities precede histological changes, as reported by Gomes et al. (5) in a murine model with conditional genetic deletion of 1 allele of desmoplakin and findings in patients carrying desmoplakin mutations. With progression of disease, adverse outcomes may be associated with more than 1 mutation or the development of biventricular dysfunction (4,6).

The diagnostic role of electrophysiologic studies is limited. Endocardial voltage mapping may be misleading because much of the scar and substrate for arrhythmias are epicardial (7). It seems unlikely that electrophysiologic studies would improve risk stratification in patients who appear to be evolving the substrate for sustained ventricular arrhythmias. Although abnormalities on signal-averaged electrocardiography are common in patients with ARVC and may support the diagnosis, they have not predicted adverse events with high specificity (8).

Uncertainty about the diagnosis, rate of progression of disease, and risk for sudden death could result in unnecessary procedures or recommendations to implant implantable cardioverter-defibrillators in the absence of any clear data to support the decision. In this issue of the Journal, te Riele et al. (9) report their evaluation of the incremental value of ECG and Holter abnormalities and CMR to assess the risk for sustained ventricular tachycardia or ventricular fibrillation in 69 patients with ARVC. The patients all had documented mutations but had never had sustained ventricular arrhythmias at entry to the study. Over a mean follow-up period of 5.8 ± 4.4 years, only 1 patient with normal ECG and Holter findings had abnormal CMR results. Among those with electrical abnormalities, defined as abnormal Holter results (frequent premature ventricular complexes or nonsustained ventricular tachycardia) or ECG characteristics of ARVC, approximately half had abnormal results on CMR. During follow-up, 16% of patients developed sustained ventricular arrhythmias, and these occurred only in patients with electrical abnormalities who also had abnormal CMR results. These data suggest that electrical abnormalities appear to precede abnormalities on CMR and that the risk for sustained ventricular arrhythmias is relatively high in patients with both electrical abnormalities and abnormal CMR findings, but the risk is low if these findings are normal or only 1 study shows abnormal results. The number of patients studied is modest, but the data are very intriguing.

te Riele et al. (9) have made a valuable contribution to our understanding of ARVC, but the study had several limitations. The baseline studies used to establish electrical and CMR abnormalities were performed when the patients were enrolled, but we do not know whether these abnormalities progressed over time, because the tests were not repeated at scheduled intervals or at the conclusion of the study. Moreover, although a mean follow-up period exceeding 5 years is acceptable for most conditions, it is a small segment of time in

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a patient who is diagnosed at a relatively young age and carries a genetic abnormality for life. What does the absence of electrical or CMR abnormalities mean for a subject 25 years of age who has a mutation associated with ARVC and is contemplating a family or career? It may be reassuring in the short term, but we need to establish appropriate guidelines for follow-up without creating undue anxiety.

One of the challenges of developing clear practice guidelines for a relatively uncommon problem with variable genetic penetrance and a low incidence of potentially fatal arrhythmias is that a large trial is required to prove the predictive value of diagnostic tests or the long-term benefits of interventions. Moreover, the costs of obtaining lifetime follow-up data and the infrastructure required to monitor it are formidable. The results reported by te Riele et al. (9) raise several questions that require a long-term, large-scale study. Their data suggest that electrical abnormalities precede the development of anatomic abnormalities. What is the interval of time before patients with electrical abnormalities develop anatomic changes detectable by CMR? Can we state categorically that carriers of desmosomal protein mutations do not require CMR until they have evidence of electrical abnormalities? Should asymptomatic carriers with both electrical and anatomic abnormalities be advised to undergo placement of an implantable cardioverter-defibrillator? Are the results of this study applicable to the broader population, or is there an unintended bias when a major referral center performs a study of this nature? A conservative approach is warranted for asymptomatic carriers who are not enrolled in studies designed to answer these difficult questions. It would be premature to alter guidelines on the basis of this study, but it would be appropriate for physicians to provide closer follow-up in patients with combined electrical and CMR abnormalities.

**REFERENCES**


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