Within the first few months of my practice, I changed the life of a young physician referred for right ventricular (RV) outflow tract ventricular tachycardia (VT) with the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). This was an uncomfortable moment, but not one nearly as bad as “the cardiologist’s worst nightmare” (1), making the opposite mistake of missing a life-threatening diagnosis due to mimicking of a much more common benign condition. How often do we make that mistake? Can it be prevented?

Since the initial description of ARVC/D, significant progress in the understanding of all aspects of this disease process has occurred. Improvements in noninvasive diagnostic strategies have been a key feature of this progress, eventually leading to the establishment of formal diagnostic criteria (2). This has led to more uniform discussion of patients with similar disease severity and has facilitated clinical discussions of risk in individual patients. Nonetheless, concern has persisted about detection of more subtle forms or “latent phase” ARVC/D, where the lack of significant RV structural abnormalities may preclude formal diagnosis but arrhythmic risk may be present.

The use of electrophysiological rather than RV imaging techniques to evaluate the diagnosis and the arrhythmia prognosis of patients who may have ARVC/D is a logical next step. In previous work by the same group, the use of RV voltage mapping was investigated in a series of 31 patients who met task force criteria for the diagnosis of ARVC/D (3). In 20 patients, detailed mapping demonstrated low-voltage areas that corresponded to wall motion abnormalities and were associated with fibrofatty replacement on biopsy and a family history of ARVC/D. However, 11 patients had no RV endocardial voltage abnormalities. This finding was associated with nonfamilial disease, inflammatory findings on biopsy, and a good prognosis.

In this issue of the Journal, Corrado et al. (4) report the results of a similar invasive evaluation in 27 patients with normal RV function and right ventricular outflow tract (RVOT) ventricular arrhythmias. This group was selected from a larger population of 89 patients with RVOT tachycardias on the basis of 1 or more high-risk characteristics: a family history of early sudden death, competition in competitive athletics (because of the possible association of aggressive aerobic exercise and RV dysplasia), pre-syncope, QRS duration in the precordial leads >110 ms, presence of late potentials on signal-averaged electrocardiography, or inverted T waves (only observed in the inferior and not in the anterior precordial leads in this experience). Importantly, none of these patients satisfied task force requirements for a diagnosis of ARVC/D before invasive study. Detailed RV electroanatomical mapping (187 ± 29 sites), programmed stimulation, and endomyocardial biopsy were performed in all patients. Catheter ablation was performed in 20 patients, guided by activation and pace mapping, and was acutely successful in 18 of 20.

Seven patients had at least 1 area in the RV marked by low-voltage bipolar electrograms (<0.5 mV) with prolonged durations and delayed components. Abnormal voltage areas were seen in the anterior portion of the infundibular free wall in all patients; additional areas were observed in the apical and inferior basal free wall in 2 patients. Ventricular tachycardia was induced with programmed stimulation in 5 of 7 patients, and pace mapping or activation mapping localized sites of origin to the free wall sites of abnormal voltage. Six of these patients had abnormal RV apical free wall endomyocardial biopsies, demonstrating fibrofatty myocyte replacement. Patients with voltage abnormalities were more likely to have precordial QRS prolongation, inducible VT with programmed stimulation, and positive signal-averaged electrocardiograms. Ablation was acutely successful in 4 of 5 patients; 2 of the patients with apparently successful and 1 with an unsuccessful ablation procedure had life-threatening ventricular arrhythmias in the 41 ± 8-month follow-up. These patients received implantable defibrillators and had subsequent appropriate therapies.

In contrast, 20 patients had normal RV voltage mapping. None of these patients had positive endomyocardial biopsies. Arrhythmias in this group were unlikely to be induced with programmed stimulation (as opposed to isoproterenol infusion) and typically arose from the septal aspect of the RVOT. None of these patients had adverse outcomes in follow-up, although 7 had recurrent ventricular arrhythmias (1 patient after an unsuccessful ablation attempt, 6 who did not have ablation).
The authors make several conclusions from these observations. First, voltage mapping appears to be an effective way of distinguishing early or concealed ARVC/D from idiopathic VT. Second, even in this concealed phase of the disease, significant electrical abnormalities may be present, with attendant risk of life-threatening ventricular arrhythmias in intermediate-term follow-up. Most electrophysiologists rely on structural assessment of the RV or electrocardiogram findings to exclude a diagnosis of ARVC/D, otherwise reserving invasive evaluation for patients with symptoms that would justify an ablation procedure. The difficulties with identification of RV fatty infiltration by magnetic resonance imaging are appreciated (5); however, as we are accustomed to thinking that arrhythmia risk follows the advent of ventricular dysfunction with LV disease, the absence of significant RV enlargement or motion abnormalities had been reassuring before this report.

This begs the question: what should the appropriate gold standard be for evaluating the strategy of voltage mapping? Voltage mapping certainly seemed to outperform imaging and electrocardiographic criteria in the present study. Although cardiac magnetic resonance imaging was not an important part of this evaluation, subtle abnormalities were observed just as often in both groups. The correlation with biopsy findings in both studies is impressive. Although one could wonder about the rare outlier (how should the patient with the abnormal voltage map and the negative biopsy be considered?), the risk associated with an abnormal voltage map was fairly high in both studies and is not well predicted by the results of programmed stimulation or apparently successful catheter ablation.

The recent observations that epicardial voltage abnormalities may be more extensive than endocardial, at least in patients with less subtle forms of the disease, adds another dimension to the uncertainty (6).

The authors admit that extension of these results to the general population of young patients with RVOT tachycardias is not possible. This group all had some aspect of risk, and the proportion of abnormal voltage maps in an unselected population is likely to be much lower. In addition, the incidence of ARVC/D is higher in the Veneto region than would be expected elsewhere. Furthermore, it is likely that all ARVC/D is not the same. Experiences comparing European and U.S. patients suggest differences in the proportion of familial/sporadic incidence, prognosis, and cause of death (i.e., proportion of sudden death vs. progressive heart failure) (7–10). The beginnings of genetic diagnosis also document many subtypes with an apparently similar phenotype. All of this underscores the importance of registries tracking the variations of this disease in large numbers of patients over longer periods of time to allow appropriate distinctions to be made (11,12).

The authors are to be congratulated for this important contribution, which will have considerable clinical impact. Unfortunately, this study underscores the treacherous and difficult nature of diagnosing serious threats to young, apparently normal patients.

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