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Editorial Comment

Improving Our Understanding of Epicardial Ventricular Tachycardia in Nonischemic Cardiomyopathy*

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Catheter ablation of ventricular tachycardia (VT) is a well-established therapeutic technique. Focal VT in structurally normal hearts can be cured by catheter ablation, and meaningful clinical results can be achieved in patients with structural heart disease who have drug-refractory arrhythmias resulting in device therapy. When hemodynamically stable and sustained, VTs can be ablated with activation and entrainment mapping. In the past several years, even hemodynamically unstable VTs have been managed by catheter ablation. This has been achieved by targeting potential arrhythmia circuits that are identified by mapping the myocardial substrate during sinus rhythm (or a paced rhythm) (1,2). The evolution of substrate-based ablation of VT has been aided by 3-dimensional electroanatomical mapping that allows localization of scars in relation to the

border zones and from areas of dense scar to normal tissue or valve continuities, resulted in a 75% freedom from recurrence at 8 months (5). Subsequently, single-center experiences and multicenter registries in post-myocardial infarction VT ablation have been published (9–15) as well as the first multicenter prospective randomized SMASH (Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia) trial (16), which demonstrated a 65% reduction in implantable cardioverter-defibrillator (ICD) therapy in patients undergoing adjunctive substrate-based ablation with ICD insertion.

While ischemia produces a predictable wavefront of necrosis (and subsequent scars) progressing from subendocardium to epicardium usually confined to a specific coronary vascular territory (17,18), scars in nonischemic cardiomyopathy have been shown to have a predilection for the mid-myocardium and epicardium (19). The current understanding of scar formation, location, and extent in nonischemic cardiomyopathy is limited compared with post-myocardial infarct scars. Analysis of explanted human hearts with dilated cardiomyopathy has revealed increased fibrosis, myocyte disarray, and membrane abnormalities (20–22). In one of the largest autopsy series published, only 14% of 152 patients with idiopathic dilated cardiomyopathy had evidence of grossly visible left ventricular (LV) scar. However, histologic examination demonstrated interstitial or replacement fibrosis in 57% of patients analyzed (23). As a result, fractionated recorded electrical activity in patients with nonischemic cardiomyopathy has been thought to result from non-uniform anisotropic conduction through myocardium separated by fibrous tissue (24).

Detailed substrate mapping studies on nonischemic patients are also limited. Myocardial scars indistinguishable from infarct scars have been demonstrated in patients with nonischemic cardiomyopathy (15). Hsia et al. (25) characterized the endocardial substrate of 19 consecutive patients with cardiomyopathy of nonischemic etiology and monomorphic VT. With a threshold of <1.8 mV for abnormal endocardium, a modest-size scar with a predilection for regions near the basal ventricle in the perivalvular region was seen in all patients. Of the 57 mapped VTs, 88% originated from these areas. Epicar-

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ventricle with local electrogram voltage characteristics obtained with point-by-point intracardiac mapping in sinus rhythm (3). With an accurate real-time representation of scar anatomy, ablation along border zone tissue to mimic surgical encircling subendocardial resection has been demonstrated to be an effective technique when VT is unsuitable for entrainment mapping (4–8). The recognition of the importance of the electrical characteristics of scars in the genesis of VTs and the characterization of their extent and location has been a major advancement in the field of VT ablation.

Substrate mapping for catheter ablation of VT and epicardial mapping. The feasibility and efficacy of substrate-based radiofrequency ablation of VT has been well-characterized in patients with post-infarct VT. In an initial experience of 16 patients, linear ablation lesions placed in areas where pacemap matches were seen, across

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dial mapping was also performed in 3 patients via the coronary sinus, where abnormal electrocardiograms were recorded along the veins. Percutaneous epicardial mapping that was pioneered by Sosa et al. (26) has now been incorporated as a regular component of VT mapping and ablation (27). Soejima et al. (28) performed endocardial mapping in 28 patients with nonischemic cardiomyopathy referred for ablation of monomorphic VT. In this report, 63% of endocardial scars were adjacent to the valve annulus. In the 7 patients that underwent epicardial mapping, all demonstrated epicardial scar, and in the 5 where combined mapping was performed, epicardial scar surface area was larger than endocardial.

The present study. In this issue of the *Journal*, Cano et al. (29) add to the working understanding of the arrhythmogenic substrate in patients with VT and idiopathic dilated cardiomyopathy. By examining endocardial and epicardial electroanatomic voltage maps in 22 patients referred for epicardial VT ablation over a 5-year period, the current study represents one of the largest published experiences of substrate characterization in nonischemic cardiomyopathy.

The primary finding of this study is that, among the 22 patients, 1 or more epicardial circuits could be identified in 18 patients. Although not statistically significant, low voltage areas were seen in 12 of 22 (54%) endocardial maps compared with 18 of 22 (82%) epicardial maps, and scar tended to be larger on the epicardial surface (46.4 ± 37.3 cm² vs. 30.2 ± 43.7 cm²). Ten patients demonstrated abnormalities confined only to the epicardium, and only 1 patient was observed to have more endocardial than epicardial scar. Patients with abnormal endocardial maps demonstrated confluent scar in the basal LV—consistent with previously published experience—whereas 16 of 18 patients with epicardial scar demonstrated a unique basal LV predilection, most often in the inferolateral LV free wall.

A strength of this study is the examination of reference control subjects to define the electrogram characteristics in the atrioventricular groove by distinguishing epicardial fat from scar (low voltage without abnormally wide, split, or late electrogram). As hypothesized, epicardial fat could be differentiated from scar by abnormal electrogram characteristics such as fractionation in addition to low voltage.

Overall, radiofrequency ablation rendered 67% of patients non-inducible at the end of the procedure, with a 71% success rate in those who underwent epicardial ablation of targeted VT. In the remaining patients, ablation was limited by phrenic nerve capture or proximity to a major epicardial coronary vessel. At a mean 18-month follow-up, 71% demonstrated freedom from VT recurrence; 14 of these 15 patients underwent epicardial ablation.

Several limitations must be noted. It must be emphasized that the cohort population described represents a highly selected group of patients who not only have nonischemic cardiomyopathy but also met criteria for ICD (21 of 22), had sustained monomorphic VT refractory to at least 1 antiarrhythmic agent, and failed previous endocardial ablation (20 of 22), leading to a strong bias toward an epicardial VT circuit

location. The mean number of previous ablation attempts was 1.8 (with up to 6 prior attempts in 1 patient). A recent study of 29 patients with nonischemic cardiomyopathy referred for VT ablation showed that 48% had scar demonstrable by delayed enhancement magnetic resonance imaging (MRI) (30). In contrast, only 2 patients required epicardial ablation for epicardially confined scar in this cohort.

However, this selection and referral bias, which is unavoidable in studies of this type, might be of importance in the bigger picture of risk stratification in nonischemic cardiomyopathy. By characterizing the electroanatomic milieu in those high-risk patients who present with monomorphic VT, we might be able to work backward in determining decreasing arrhythmic risk. Although the present study is heavily biased toward the patients with discrete scars, further understanding of the other patients with nonischemic cardiomyopathy without discrete scars and their respective arrhythmic burden is necessary. A patient's candidacy for substrate-guided ablation might diminish between patients with and without scars due to progressively decreasing target areas. Furthermore, the baseline risk for ventricular arrhythmias might be similarly diminished (31). In this study, low-amplitude signals were classified into 3 groups: wide (>80 ms), split (20 ms isoelectric segment), and late (outside QRS). Almost 50% of the abnormal electrograms in the epicardial scar were wide, split, or late. The relationship of these potentials to conducting channels or isthmuses was not reported and is not well understood in patients with dilated cardiomyopathy.

An additional limitation lies in the exclusionary nature of classifying patients as “nonischemic” or “idiopathic dilated.” In the current study, nonischemic cardiomyopathy was defined as the absence of coronary stenosis $>75\%$, prior infarction, valvular abnormalities, and known causes of dilated cardiomyopathy, including arrhythmogenic dysplasia/cardiomyopathy. In reality, idiopathic nonischemic cardiomyopathy is likely to represent the residual myocardial substrate from a heterogeneous group of etiologies, such as post-viral, toxin-associated (cocaine, alcohol), occult sarcoidosis, diabetes mellitus, and long-standing hypertensive heart disease. Additionally, many patients might have a mixed etiology of cardiomyopathy, which can include a component of coronary artery disease. Spasm or embolic infarction can never be ruled out with clinical certainty.

The lack of pathologic correlation in the study population is another limitation. In the study methodology, voltage maps serve as the modality being tested as well as the gold standard. Electroanatomic mapping has not been validated with gross and histopathologic correlation in nonischemic cardiomyopathy. Because the authors state that several of the patients went on for a transplant, confirmatory pathologic data would be invaluable to confirm areas of scar and fat. Furthermore, an MRI would also have been helpful to correlate these causes of low voltage, although the current standard of care still dictates avoidance of MRI in those with implanted devices.

Future prospects. Although there are many unanswered questions regarding this population of patients, the current study by Cano et al. (29) is an important contribution to our understanding of one end of a disease spectrum. Such questions include: What determines the extent of fibrosis in nonischemic cardiomyopathy? Why do some areas of low voltage have late potentials, whereas others do not? Why is there a predilection for scar on the basal inferolateral LV? Is it possible that circumflex infarctions, which tend to be less evident on a 12-lead electrocardiogram, contribute to basal scars? Does the finding of a perivalvular scar support a post-viral etiology of idiopathic dilated cardiomyopathy? A recent study involving MRI in acute myocarditis demonstrated epicardial delayed enhancement in 91% (21 of 23) of patients with inferolateral midventricular predominance (32).

Further studies in patients with nonischemic cardiomyopathy are needed to improve our understanding of their electrophysiologic substrate. Such studies, which will help us interpret the “electrical footprint” left behind by myocardial diseases that result in cardiomyopathy, will provide additional insights for improving our risk prediction and therapeutic strategies.

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