The basis for arrhythmogenesis in patients with nonischemic cardiomyopathy and ventricular tachycardia (VT) needs further elucidation. Cardiac arrest and/or nonsustained VT are common arrhythmia presentations in the setting of nonischemic cardiomyopathy, with sustained monomorphic VT being relatively uncommon.1,2 Importantly, bundle-branch reentrant VT is identified as the VT mechanism in a significant percentage of patients with monomorphic VT in the setting of nonischemic cardiomyopathy.3,4 However, even in patients with nonischemic left ventricular (LV) or right ventricular (RV) cardiomyopathy, the majority of VT appears to originate from the myocardium and is not due to bundle-branch reentry.4–11 Detailed substrate, activation, and entrainment mapping has begun to provide some valuable clues related to the mechanism and pathophysiology of scar-based VT in the setting of nonischemic cardiomyopathy resulting from a variety of causes.4–11 Although not focusing on VT after valve surgery, these data have been helpful in identifying likely regions of origin for VT and facilitating ablative therapy in other nonischemic settings.

Lessons Learned From Ablation of VT After Valve Surgery

When dealing with uncommon disease processes, one looks to centers with sizable clinical experience to review their results and provide important insight. In this issue of Circulation, the report by Eckart and colleagues12 answers that charge. Six years of clinical experience with VT ablation in this setting have allowed the authors to identify 20 patients who developed VT after prior cardiac valve surgery and underwent catheter ablation therapy. Importantly, most of the patients demonstrated mildly to moderately depressed LV function with a median LV ejection fraction of 45%. Characterization of the substrate, mechanism, and outcome of ablative therapy provides important insight in terms of pathogenesis. Such detailed information should be compared with findings at the time of VT ablation in a variety of other nonischemic cardiomyopathies to attempt to identify common and potentially important pathophysiological links.4–11

Indeed, the study by Eckart and colleagues is modestly handicapped by its retrospective study design. Details of the preoperative status of LV function and the surgical intervention were unavailable, making it difficult to determine whether some abnormalities preceded or were created by surgical incisions, venting, or the like. The timing of the “late” onset of VT as it relates to the surgery also is probably much shorter than the described 12 years for the second mode of presentation timing. Of note, 12 of the 16 patients who underwent ablation late after surgery because of VT in the present report already had an implantable cardioverter-defibrillator in place for a median of 4.5 years, presumably for a documented arrhythmia episode in most.12 Nevertheless, a distinction between early, <1 month, and late, >1 to 20 years, is valid and somewhat similar to the bimodal distribution of VT after myocardial infarction. The distinction also is supported by the observed differences noted in the electrophysiology laboratory between the 2 patient groups. Patients presenting early after valve surgery with VT were more likely to have bundle-branch reentrant VT or not have VT inducible at the time of electrophysiological evaluation and were not likely to have spontaneous VT during follow-up if VT was not inducible. These differences suggest that the VT early after valve surgery may be linked to acute inflammation and is more likely to be transient. A persistent substrate for myocardial reentry appears to be lacking in most patients.

The seminal observations made by Eckart and colleagues are related to the detailed characterization of the substrate for and mechanisms of VT and the outcome of catheter ablation in the patients presenting with VT ablation late after valve surgery.12 Although a quantitative assessment of scar burden was not provided, patients demonstrated areas of scarring as indicated by the confluent areas of recorded low-amplitude bipolar electrogram voltage. For 14 of the 17 patients who presented with VT late after surgery, the authors also indicate that a scar-related reentrant mechanism was suggested by the response to stimulation during VT. Importantly, the outcome reported with VT catheter ablation was excellent with respect to both VT control and risk.12 Caution should be applied, however, in assuming that these results can be duplicated beyond very experienced centers. Catheter entrapment in disk valves, resulting in acute valve dysfunction, and disruption of calcific porcine valves, resulting in serious embolic phenomena, must be recognized as potential life-threatening risks with catheter ablation in this setting.
One of the most remarkable findings of the study by Eckart and colleagues was the observation related to the distribution of the scar substrate. Nearly two thirds of the patients with reentrant VT showed endocardial scar and a VT origin in a perivalvular distribution. Even more remarkable was the fact that in 8 of the 9 patients with perivalvular scar, the scar surrounded the valve replaced at the time of surgery. A nonperivalvular substrate was present in the minority of patients. As the authors note, the VT associated with “scar” or low-bipolar-voltage areas in the nonperivalvular distribution may have been related to a prior unrecognized coronary embolic event or a surgical incision in the ventricle. Because details of the medical and surgical histories before referral for ablation were unavailable, these remain important possibilities. The skepticism regarding a direct relationship between valve replacement and nonperivalvular scar distribution in the pathogenesis of VT is probably justified. An even greater direct pathophysiological link between the perivalvular scar distribution and valve surgery when VT is manifest late post valve surgery is suggested for the remaining patients.

**Comparison of Findings With Other Nonischemic Cardiomyopathies**

The perivalvular distribution of low-voltage areas consistent with scar in patients who manifest unimorphic VT after valve surgery is remarkably similar to the location of abnormalities recorded in a variety of other nonischemic cardiomyopathies when evidence of sustained monomorphic VT is present (the Figure). Patients with VT and idiopathic LV cardiomyopathy, RV cardiomyopathy/dysplasia, and chronic chagasic heart disease all demonstrate large areas of low bipolar voltage surrounding the valves, with the low-voltage abnormalities extending from these perivalvular regions toward the more apical segments of the RV or LV. Pathological evidence of scar in the anatomic distribution of these low-bipolar-voltage areas has been confirmed in selected patients. Even in less well-investigated disorders such as giant cell myocarditis and sarcoidosis, a predilection for basilar, perivalvular expression of endocardial low-voltage areas has been identified (the Figure). More recently, an epicardial perivalvular distribution of scar also has been identified in selected patients with VT in the setting of a nonischemic cardiomyopathy. Certainly, exceptions to this perivalvular distribution have been noted, and the involvement can be patchier and more diffuse, but these cases do not appear to represent the norm.

**A Common Pathogenesis for the VT Substrate in Nonischemic Cardiomyopathies**

It is important to attempt to identify the common pathogenesis that explains why seemingly distinct cardiac disease processes result in a similar substrate for sustained unimorphic VT. Why the perivalvular region predominates as the primary region for the fibrotic changes remains speculative. Could it be simply an overexpression of a healing response to a more generalized or, in the case of valve surgery, localized inflammatory response? Could fibroblasts simply be more available to be turned on in proximity to the valve structures? Because the perivalvular scarring process appears to occur in selected individuals, it would strongly suggest a unique, genetically determined primary myocardial abnormality, a unique but common insult, or both. Investigation in RV
cardiomyopathy/dysplasia has identified genetically determined desmoplakin and plakophilin abnormalities that appear to result in the structural abnormalities that play role in the disease pathogenesis.\textsuperscript{14,15} It has been suggested that perhaps in some patients with RV cardiomyopathy/dysplasia, an environmental pathogen may trigger an acute inflammatory response that initiates the expression of the genetically determined abnormalities.\textsuperscript{7} The associated marked hemodynamic stresses at the time of the acute inflammation might result in the aneurysmal out-pouching at the RV apex that is commonly observed. A postinflammatory fibrotic reaction consistently extending from the perivalvular tricuspid and/or pulmonic valve toward the apical region of the RV free wall might explain the nearly uniform substrate identified in patients who manifest VT.\textsuperscript{7} Could desmosomal or other structural protein abnormalities also play a role in other nonischemic disease processes more commonly manifest in the LV? A similar manifest pathogenesis with apical aneurysm and perimitrval valve endocardial and epicardial scar appears as the substrate for monomorphic VT in the setting of chronic chagasic heart disease.\textsuperscript{11} Ablative therapy, which originally focused only on the surgical removal of the apical aneurysm, has shifted to endocardial and epicardial catheter ablation, which is focused on the region of the perivalvular scar where the VT circuit resides in chronic chagasic heart disease.\textsuperscript{11} Additional evidence pointing to a common thread in the pathogenesis of monomorphic VT in different nonischemic cardiomyopathies includes the occasional patient who demonstrates RV and LV VT, peritricuspid and mitral valvular electrogram abnormalities, and biventricular cardiomyopathy.\textsuperscript{7} One could imagine in patients with the appropriate genetic predisposition that a significant amount of perivalvular inflammation or wall stress from a variety of triggers might result in a progressive perivalvular fibrotic reaction. One has only to see a dramatic skin keloid formation or the palmar/plantar keratosis in patients with Naxos disease to recognize that a similar type of intracardiac stress response might be manifest by the development of perivalvular cardiac fibrosis in a patient genetically predisposed.\textsuperscript{15} Further investigations are needed to determine the incidence of the perivalvular fibrotic response in a variety of nonischemic cardiomyopathies to determine whether the response is indeed specific for the development of VT and to identify similar or other genetic markers for the defined structural abnormalities. Efforts to document with sophisticated imaging techniques the time course for the development and/or progression of the macroscopic fibrosis also are needed. This information may have dramatic clinical implications if indeed the extensive fibrotic reaction represents an overexpression of a healing response or response to mechanical stress that can be predicted or identified early in the process in selected individuals and aborted with appropriate drug intervention.

**Unique Substrate for Monomorphic VT in Nonischemic Cardiomyopathy**

It also is important to attempt to determine what distinguishes patients who present with monomorphic sustained VT from other patients with cardiomyopathic processes and either no arrhythmia or a different ventricular arrhythmia presentation such as nonsustained VT or cardiac arrest. The distinct perivalvular endocardial or epicardial scar distribution commonly noted when unimorphic VT is present is even more remarkable when one notes that more diffuse midmyocardial fibrosis has been documented with cardiac magnetic resonance imaging studies in many patients with nonischemic cardiomyopathy.\textsuperscript{16} This midmyocardial fibrosis may be the more typical pattern of macroscopic fibrotic changes in patients who have nonischemic cardiomyopathy and a lower likelihood of sustained monomorphic VT. An adequate substrate for monomorphic VT may simply be a matter of overall scar burden, with those patients with endocardial and epicardial manifest fibrosis having more advanced disease states. However, this appears unlikely or least oversimplified because many patients with scar-related VT, including those with VT after valve surgery, have only modestly depressed LV function, suggesting a more limited or focal disease process.\textsuperscript{12} Although the overall degree of LV dysfunction may be modest, it is clear that patients with monomorphic VT manifest greater endocardial scar burden than those patients with nonischemic cardiomyopathy who present with nonsustained VT or cardiac arrest.\textsuperscript{2,8} Perhaps in the latter patients a more diffuse microscopic process exists or, in selected individuals, midmyocardial macroscopic fibrosis predominates. These patterns of fibrosis are less likely to produce endocardial bipolar electromogram abnormalities, although they may result in more myocardial dysfunction. Furthermore, this type of scar distribution may be less likely to create a sizable area of slow conduction that might support a sustained monomorphic reentrant VT but still may produce an adequate substrate for more unstable or shorter-lived arrhythmias. It remains to be determined whether the overall (endocardial, midmyocardial, and epicardial) macroscopic scar burden truly is greater in patients who manifest monomorphic VT. It is equally possible that the specific distribution of scar is more important, with fibrotic changes involving endocardial, midmyocardial, and frequently epicardial perivalvular regions creating the roadmap within a 3-dimensional matrix for sustained monomorphic VT. What is clear from the excellent long-term results with endocardial catheter ablation is that at least a component of the reentrant circuit is endocardial in patients with prior valve surgery and scar-related VT.\textsuperscript{12} This is important information in planning ablative therapy because percutaneous epicardial access after prior surgery may be limited.

Like many publications of merit, the work by Eckart and colleagues serves a dual purpose. It clearly provides a valuable clinical guide for the approach to and anticipated success of catheter ablative therapy in patients with valvular heart disease and VT. Just as important, it also provides, through an assessment of the VT mechanism and substrate, clues to cardiac disease pathogenesis that both raise important questions and suggest a common link with other nonischemic cardiomyopathies that can create the substrate for sustained VT. The questions raised need to be answered and the links explored.

**Disclosures**

None.
References


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