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EDITORIAL COMMENT

Sympathetic Denervation to Treat Refractory Ventricular Tachycardia

Do We Have the Nerve?*

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Implantable cardioverter-defibrillators (ICDs) have been proven to prolong life in patients with cardiomyopathy and reduced ejection fraction; however, the major morbidity associated with ICDs has been recurrent ICD shocks for ventricular tachycardia or ventricular fibrillation (VT/VF). Treatment for VT/VF typically involves suppression with antiarrhythmic drugs, catheter ablation, or both. Catheter ablation has made tremendous strides in the past 2 decades because of improvements in substrate modification techniques for poorly tolerated VT, hemodynamic support in patients with severely depressed ejection fraction, epicardial ablation approaches, surgical ablation, and more advanced mapping and ablation technologies. Yet recurrence rates after VT ablation in several prospective studies still approach and sometimes exceed 50% (1,2). Patients often require transfer to specialized centers for VT management, yet many have end-stage cardiomyopathy or VT/VF that is not amenable to ablation because of deep intramural circuits or multiple pleomorphic VTs. Some are not candidates for cardiac transplantation because of age, comorbidities, or lack of social support. Treatment options are limited for these patients, who can remain hospitalized in intensive care units and receive multiple intravenous antiarrhythmic agents and sedatives.

Left cervical sympathetic denervation (CSD) as a therapeutic modality for treating angina and VT/VF was first described by Jonnesco (3) and has gained wider acceptance for use in patients with long-QT syndrome and recurrent arrhythmias (4,5). Investigators at the University of California-Los Angeles (UCLA) have pioneered the use of CSD in patients with structural heart disease and recurrent VT/VF. They have nicely demonstrated in translational animal models that cervical CSD leads to a decrease in dispersion of repolarization in the left ventricle and decreases inducibility of VT. Small case series in patients from the same group have demonstrated a reduction in VT episodes after CSD, with a better outcome after bilateral compared with left CSD (6). Recent work from Doytchinova et al. (7) found that sympathetic activity measured from skin electrodes increased in 73% of patients before episodes of VT, and bilateral stellate blockade inhibited sympathetic activity. The accumulated evidence, therefore, strongly supports a role of sympathetic neuromodulation in controlling refractory VT; however, the generalizability of such single-center studies is unclear.

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In this issue of the *Journal*, Vaseghi et al. (8) report outcomes after CSD in patients with refractory VT/VF. The team from UCLA collected retrospective data from 5 international sites performing CSD between 2009 and 2016. Importantly, these centers were all identified as routinely using CSD for treatment of refractory VT. The study included 121 consecutive patients with structural heart disease, most of whom had dilated nonischemic cardiomyopathy. The indications for sympathectomy and concomitant antiarrhythmic therapies were left to the discretion of the

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attending physicians at each institution. Patients were followed up for a mean of 1.5 years after sympathectomy. The majority of patients (75%) had a history of VT storm, with a median of 2 prior catheter ablations for VT in 66% of patients.

Complications related to CSD were infrequent, primarily related to the surgery, with 4% developing ptosis or Horner syndrome acutely. The international authors found that freedom from sustained VT, ICD shocks, cardiac transplantation, or death was 50% at 1 year and 39% by the end of follow-up. ICD shocks were reduced from 18 ± 30 in the year before CSD to 2.0 ± 4.3 during follow-up. Risk factors associated with recurrent VT or ICD shocks included advanced New York Heart Association (NYHA) functional class and a longer VT cycle length (>400 ms). Advanced NYHA functional class and a left-sided–only CSD were independently associated with death or cardiac transplantation. At the end of follow-up, 26% of patients had died and another 10% had undergone cardiac transplantation.

This retrospective series is fraught with many of the usual limitations of retrospective data collection. The indications and procedures were heterogeneous. The vast majority of patients (71%) had dilated cardiomyopathy. At some centers, CSD was offered before VT ablation because of polymorphic VT or the "high cost" of VT ablation (primarily in Columbia or India), whereas the remainder had CSD performed only after unsuccessful VT ablation. Despite data from the UCLA group that bilateral CSD is more effective, 19% of patients underwent only left CSD. And despite a reasonable outcome, with 58% of patients free of ICD shocks at 1 year, 68% of patients were still taking antiarrhythmic drugs, one-fourth had died, and one-tenth had undergone transplantation by the end of the study, which highlights the management challenges in this very sick group of patients.

What have we learned from this international database? The data largely confirmed previous reports from the UCLA group. The major findings were that CSD works best when performed bilaterally, when used for VT that is fast and polymorphic, and in patients who do not have end-stage cardiomyopathy (NYHA functional class IV). This information is very useful. The patient with an incessant, slow monomorphic VT is unlikely to benefit from CSD and might be offered surgical ablation, alcohol ablation, needle, or bipolar ablation. Those with rapid and polymorphic VT might move more quickly to CSD, reserving repeat ablation for recurrent slower VTs. Unfortunately, given the heterogeneous indications and population, it is still not quite clear where CSD fits in the VT therapy armamentarium. Should CSD be performed after the first unsuccessful catheter ablation? Or only as a last resort after multiple failed ablations? Is CSD more suited to dilated cardiomyopathy patients? Are there VT electrocardiographic morphology predictors of those who might do better with CSD? Can response to thoracic epidural anesthesia or other therapies help predict success with CSD? And what are the long-term implications of bilateral sympathetic denervation? The authors stated that collateral innervation mitigated the deleterious effects of CSD, but we have few data on heart rate response to exercise and sudden death late after CSD. Sympathetic innervation of the heart likely has some teleological benefit, and bilateral denervation could have unanticipated consequences.

Nevertheless, we are indebted to the authors for additional insight into this unique therapy. It is fairly boilerplate to thank authors for their contribution when writing an editorial. But in this case, Vaseghi et al. (8) have really set the standard for bringing a research concept to clinical practice. They performed extensive preclinical research in animal models that demonstrated the mechanisms whereby CSD might reduce VT, via lengthening of action potential duration, reduction in repolarization heterogeneity, and reduction of VT inducibility. They then published small case series of CSD in humans with refractory VT and few interventional options. Further series elucidated the benefit of bilateral over unilateral sympathectomy. Now, they have put together a multicenter retrospective study. The clear next step is a prospective randomized controlled trial, which the authors have initiated. It is a remarkable demonstration of the appropriate steps to be taken toward scientific development of new therapies and the contributions that can be made by clinician scientists. In too many cases, new interventional therapies are brought into clinical practice without rigorous scientific underpinnings.

For now, we think it is reasonable to consider CSD in patients with NYHA functional class I to III heart failure and refractory VT after 1 or 2 catheter ablations, particularly in patients with fast, polymorphic VT. It makes sense to perform this thoracoscopic procedure before moving on to advanced therapies such as transplantation or ventricular assist devices. We look forward to the results of prospective randomized studies from this group to further define the role of CSD in treating patients with refractory VT.

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