Cardiac sympathectomy for the management of ventricular arrhythmias refractory to catheter ablation

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BACKGROUND Catheter ablation is now a mainstay of therapy for ventricular arrhythmias (VAs). However, there are scenarios where either physiological or anatomical factors make ablation less likely to be successful.

OBJECTIVE The purpose of this study was to demonstrate that cardiac sympathetic denervation (CSD) may be an alternate therapy for patients with difficult-to-ablate VAs.

METHODS We identified all patients referred for CSD at a single center for indications other than long QT syndrome and catecholaminergic polymorphic ventricular tachycardia who had failed catheter ablation. Medical records were reviewed for medical history, procedural details, and follow-up.

RESULTS Seven cases of CSD were identified in patients who had failed prior catheter ablation or had disease not amenable to ablation. All patients had VAs refractory to antiarrhythmic drugs, with a median arrhythmia burden of 1 episode of sustained VA per month. There were no acute complications of sympathectomy. One of 7 patients (14%) underwent heart transplant. No patient had sustained VA after sympathectomy at a median follow-up of 7 months.

CONCLUSION Because of anatomical and physiological constraints, many VAs remain refractory to catheter ablation and remain a significant challenge for the electrophysiologist. While CSD has been described as a therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, data regarding its use in other cardiac conditions are sparse. This series illustrates that CSD may be a viable treatment option for patients with a variety of etiologies of VAs.

KEYWORDS Ventricular arrhythmia; Catheter ablation; Cardiac sympathetic denervation; Autonomics; Ventricular tachycardia; Ventricular fibrillation; ICD shocks

Introduction
The use of implantable cardioverter-defibrillators (ICDs), antiarrhythmic drugs, and finally catheter-based ablation techniques are the standard of care for patients with recurrent ventricular arrhythmias (VA) and ICD shocks.1–4 Catheter ablation has been shown to reduce ICD shocks and electrical storm in comparison to a medical therapy strategy,5,6 and mortality may be reduced in patients who respond to ablation.7 However, despite advances in electroanatomic mapping and catheter technology, there remains a subset of patients with VAs who do not respond to catheter ablation. In some well-defined instances, this is due to either anatomical or physiological limitations. Fundamentally, in order for catheter ablation to be successful, either the origin or critical isthmus of a ventricular tachycardia (VT) circuit must be relatively constant and anatomically accessible. When these 2 conditions are not met, it is unlikely that catheter ablation will result in long-term success. For instance, VAs arising from multiple points of automatic activity may not be amenable to ablation. Other VAs may prove challenging to ablate owing to anatomical constraints, such as those arising from either intramyocardial circuits in the intraventricular septum or papillary muscles,6 or difficult-to-access epicardial sites such as the left ventricular (LV) summit,7 areas insulated by pericardial fat, sites adjacent to coronary arteries, or owing to pericardial adhesions from prior cardiac surgery (Figure 1).

It has long been described that the autonomic nervous system plays a critical role in the initiation and maintenance of VAs.8 VAs themselves may also modulate sympathetic inputs to the heart.5 Cardiac sympathetic denervation (CSD) has been demonstrated to increase the ventricular fibrillation (VF) threshold.9 While the use of CSD has an established role in the treatment of some forms of congenital long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT),10–13 its utility in the treatment of other forms of VA is not as well defined.14 We present our experience with CSD in patients with recurrent VAs despite attempts at treatment with antiarrhythmic drugs and catheter-based ablation. These cases illustrate the potential utility of sympathectomy in cases where ablation proves difficult.
For catheter ablation procedures, substrate mapping was performed during sinus rhythm or right ventricular pacing if pacemaker dependent. LV access was obtained via a transseptal or retrograde aortic approach. Intravenous heparin was administered with a target activated clotting time of >300 seconds during LV endocardial access. Epicardial access was obtained by the technique described by Sosa et al as felt to be appropriate by the operator on a case-by-case basis. A bidirectional 8-F mapping and ablation catheter with continuous saline irrigation and force sensing (ThermoCool SmartTouch, Biosense Webster, Inc., Diamond Bar, CA) was used for mapping and ablation. An 8-F phased-array intracardiac echocardiography catheter with a magnetic location sensor (SoundStar eco 8F GE, Biosense Webster, Inc.) was used to create baseline contours of the right ventricle, LV, papillary muscles, and outflow tracts; assist catheter manipulation; and monitor for adequate contact and lesion formation. Voltage mapping was performed utilizing the local bipolar electrogram (EGM) and unipolar EGM with annotation of local abnormal, split, and fractionated EGMs. An isochronal map was created during sinus rhythm by mapping to the offset of the local EGM, similar to the approach recently described. The region of densest isochrones within the area of bipolar scar was delineated as having the slowest conduction during sinus rhythm. Programmed ventricular stimulation was performed in every case, and induced arrhythmias were compared with those occurring spontaneously. If VT was induced and hemodynamically well tolerated, activation and entrainment mapping were performed during VT, with annotation of mid-diastolic potentials and areas corresponding to the critical isthmus. If there was no inducible VT or the tachycardia was unstable, an empiric substrate-guided ablation was performed, guided by isochronal mapping. At the end of ablation, ventricular pacing was delivered with 2 drive trains with up to at least 3 extrastimuli in at least 2 sites in both the left and right ventricles.

Results
Of ~250 patients undergoing attempted catheter ablation of VT, 7 patients were identified who underwent CSD between March 2013 and February 2017. Case details are presented below and summarized in Table 1. The median arrhythmia burden before sympathectomy in these cases was 1 episode of sustained VA per month. Six of 7 patients (86%) underwent bilateral sympathectomy. No patient had recurrent sustained VAs at a median

Figure 1  Challenging to ablate origins of ventricular arrhythmia. Schematic of the heart demonstrating sites that pose a challenge to ventricular tachycardia ablation. The 2 main anatomical constraints to ventricular tachycardia ablation are sites deep within the myocardium, such as those in the interventricular (IV) septum or papillary muscles, and sites with difficult epicardial access such as those covered by other structures, insulated by epicardial fat, or near coronary vessels. The heart is shown with the anterior wall of the left and right ventricles cut away. The anterior left atrium as well as deemed necessary by the attending surgeon.

Methods
We identified all patients referred for CSD with an indication other than long QT syndrome or CPVT. Patients with a history of recurrent VAs despite therapy with antiarrhythmic drugs as well as attempted catheter ablation were identified. Patients were identified from the case records of electrophysiologists performing VT ablation procedures at our center. Medical records were reviewed for history, antiarrhythmic drug use, prior catheter ablation procedures, procedural details, and follow-up. Patients were considered free of recurrence if they had not experienced a clinical recurrence, appropriate ICD shock, or monitored episode of sustained VA. All patient data were de-identified to protect patient privacy. Preoperative arrhythmia burden was obtained from chart review including review of any available interrogations from implanted cardiac electronic devices or external monitors. Follow-up of arrhythmia-related outcomes was assessed by chart review. The most recent follow-up data for all patients were reported.

Sympathectomy was performed using a thoracoscopic approach with incisions made in the mid-axillary line at the fifth and third intercostal spaces. Using electrocautery, the sympathetic chain was divided over the second and third ribs. The sympathetic chain was divided bilaterally in all but 1 case as described in the results. Chest tubes were placed intraoperatively as deemed necessary by the attending surgeon.

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<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (y)</th>
<th>Cardiac substrate</th>
<th>Arrhythmia</th>
<th>Preoperative arrhythmia burden</th>
<th>Mechanism</th>
<th>Antiarrhythmic drugs failed</th>
<th>Catheter ablation procedures</th>
<th>Sympathectomy</th>
<th>Months free of sustained VA postsympathectomy</th>
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<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>Normal</td>
<td>Multiple VT morphologies</td>
<td>Frequent NSVT with exertion</td>
<td>Increased automaticity</td>
<td>Sotalol</td>
<td>1</td>
<td>Left only</td>
<td>49</td>
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<td>2</td>
<td>53</td>
<td>HCM</td>
<td>VF</td>
<td>3 episodes of VF in 2 mo previously</td>
<td>Initiated by short coupled fascicular PVC</td>
<td>Amiodarone</td>
<td>2</td>
<td>Bilateral</td>
<td>10</td>
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<tr>
<td>3</td>
<td>50</td>
<td>ICM (SCAD)</td>
<td>VF</td>
<td>2 episodes of VT/VF in 3 mo previously</td>
<td>NA</td>
<td>Amiodarone, sotalol, mexiletine</td>
<td>1</td>
<td>Bilateral</td>
<td>8</td>
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<td>4</td>
<td>36</td>
<td>NICM</td>
<td>VT</td>
<td>2 episodes of VT in 2 mo previously</td>
<td>Reentry</td>
<td>Amiodarone</td>
<td>2</td>
<td>Bilateral</td>
<td>3</td>
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<tr>
<td>5</td>
<td>54</td>
<td>Normal</td>
<td>Idiopathic VT</td>
<td>7 episodes of VT in 6 mo previously</td>
<td>Triggered activity</td>
<td>Sotalol</td>
<td>1</td>
<td>Bilateral</td>
<td>7</td>
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<tr>
<td>6</td>
<td>70</td>
<td>ICM</td>
<td>MMVT and PMVT</td>
<td>1 shock and &gt;200 episodes of NSVT in 3 mo previously</td>
<td>Reentry; ischemia</td>
<td>Sotalol, quinidine, mexiletine</td>
<td>1</td>
<td>Bilateral</td>
<td>2</td>
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<tr>
<td>7</td>
<td>64</td>
<td>NICM (ARVC)</td>
<td>VT</td>
<td>4 episodes of VT in 1 mo previously</td>
<td>Reentry</td>
<td>Amiodarone, quinidine, mexiletine</td>
<td>2</td>
<td>Bilateral</td>
<td>NA OHT</td>
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</table>

ARVC = arrhythmogenic right ventricular cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICM = ischemic cardiomyopathy; MMVT = monomorphic ventricular tachycardia; NA = not applicable; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; OHT = orthotopic heart transplant; PMVT = polymorphic ventricular tachycardia; PVC = premature ventricular contraction; SCAD = spontaneous coronary artery dissection; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.
follow-up of 7 months (interquartile range 2–9 months). There were no acute complications. One patient (case 7) underwent heart transplant shortly after sympathectomy; the decision to list for transplant was made before sympathectomy, and an organ became available shortly after the operation. Transplant was not performed for recurrent arrhythmia after sympathectomy; however, this patient’s transplant limits our ability to assess her clinical response to sympathectomy.

Case 1: Sympathetically mediated idiopathic VT
A 29-year-old man presented with palpitations and nonsustained VT during exertion (Figure 2). He had no evidence of structural heart disease. Despite treatment with sotalol, VA significantly limited his activity and he underwent electrophysiology study, which revealed multiple VT morphologies that were seen only with infusion of isoproterenol. Atrial and ventricular extrastimuli did not induce arrhythmia. As there was no consistent morphology to map, ablation was not performed. He was referred for left CSD 2 months later. He has had no subsequent VAs in the 4 years after his procedure and has been able to resume normal activity including running marathons. This patient may have CPVT; however, typical bidirectional VT was never seen. Genetic testing for this condition has not been performed.

Case 2: Premature ventricular contraction–induced VF
A 53-year-old man with coronary artery disease and hypertrophic cardiomyopathy experienced cardiac arrest secondary to VF and underwent implantation of an ICD. He experienced an ICD shock for VF 6 months later. Coronary angiography revealed no obstructive disease, and he was treated with sotalol. He experienced another shock for VF 10 months later and was treated with mexiletine. On review of his ICD diagnostics (Figure 3), his VF was reliably induced by a short-coupled premature ventricular contraction (PVC) and this initiating PVC was targeted for ablation originating from the left anterior fascicle with good postprocedural suppression of his PVC. He suffered recurrent VF with a similar initiation pattern, and a second ablation procedure was attempted but limited by lack of mappable PVCs. VF recurred shortly after his procedure, and he was referred for bilateral CSD. This procedure was performed without complications, and he has not had recurrence of VAs in the 12 months since his procedure.

Figure 2  Stress testing case 1. A: Preoperative exercise treadmill test results demonstrating exertional monomorphic ventricular tachycardia. B: Postoperative exercise test results. The patient exercised to stage 7 on a standard Bruce protocol with no ventricular arrhythmia.

Figure 3  Premature ventricular contraction–induced ventricular fibrillation. Recorded episode from the implantable cardioverter-defibrillator demonstrating 2 premature ventricular contractions (arrows), the second initiated ventricular fibrillation.
Case 3: VF in ischemic substrate
A 50-year-old woman with a history of spontaneous left anterior descending coronary artery dissection and resultant anterior infarction developed recurrent monomorphic VT with a tachycardia cycle length of 250–280 ms. She underwent ablation targeted to her apical scar. She did not have recurrent VT, but developed VF resulting in ICD shocks 2 months later. Coronary angiography revealed patent bypass graft. She was unable to take amiodarone because of thyroid toxicity and mexiletine resulted in gastrointestinal tract upset. She underwent bilateral CSD during that hospitalization. She tolerated the procedure well and was discharged on postoperative day 1 without complications. She has not had recurrence of VA in the 10 months since her procedure.

Case 4: VF in nonischemic substrate
A 36-year-old man with nonischemic cardiomyopathy presented with VT despite therapy with amiodarone. He underwent endocardial ablation only (anatomy was not amenable to percutaneous epicardial access because of “funnel chest”) with targeting of substrate in the perimitral distribution. Six months later, he had recurrence of VT, resulting in syncope and ICD shocks. Repeat hybrid VT ablation was performed with surgical epicardial access and ablation over the right ventricular epicardium. One month later, he developed VF requiring an ICD shock. He underwent bilateral CSD, tolerated the procedure well, and was discharged on postoperative day 1 without complications. He has continued to have a low burden of nonsustained VT, but has not required ICD therapies in the 4 months since his procedure.

Case 5: Idiopathic VT originating from the cardiac summit
A 54-year-old man with hypertension and diabetes but no structural heart disease developed palpitations associated with presyncope. He presented to an outside emergency department in stable VT. He was transferred to our medical center where he was taken for ablation. Morphology was felt to be consistent with an epicardial origin at the LV summit (see Figure 1). Activation mapping was consistent with diffuse breakthrough in the anteroseptal right ventricular outflow tract and septal left ventricular outflow tract, with the earliest site of activation being in the proximal anterior interventricular vein. Ablation was performed at the sites of earliest activation in the great cardiac vein and aortic cusps with suppression of VT (Figure 4). After several months, he had recurrence of VT during exertion. His VT was responsive to treatment with metoprolol and sotalol, but he did not tolerate β-blockers owing to fatigue. He underwent bilateral CSD, tolerated the procedure well, and was discharged on postoperative day 1 without complications. He has not had recurrence of VAs in the 8 months since his procedure.

Case 6: Monomorphic and polymorphic VT in the setting of unrevascularizable coronary artery disease
A 70-year-old man with a history of coronary artery disease and prior bypass grafting developed recurrent VT resulting in ICD shocks despite treatment with amiodarone. Mapping and ablation were attempted endocardially (epicardial access was not obtained because of prior sternotomy). He developed polymorphic VT 7 months later and was treated with sotalol. Polymorphic VT recurred 1 month later, and he was transitioned to quinidine and mexiletine. His ICD was upgraded to a cardiac resynchronization therapy with defibrillator device for left bundle branch block and progressive heart failure. Six months later, he developed retrosternal chest pressure and underwent stress testing, which was interrupted as he developed symptomatic VT. Coronary angiography revealed severe native vessel disease and occlusion of vein grafts to his right coronary artery and circumflex territories that could not be revascularized. He developed recurrent monomorphic VT that was well tolerated, and medical therapy was continued. However, he eventually developed severe nausea and mexiletine was discontinued. After discontinuing mexiletine, his recurrent VT became symptomatic. He underwent bilateral CSD, tolerated the procedure well, and was discharged on postoperative day 1 without complications. He has not had recurrence of VAs in the 2 months since his procedure.

Case 7: VT originating from intramyocardial circuit in interventricular septum
A 64-year-old woman with arrhythmogenic right ventricular cardiomyopathy presented with VT storm resulting in ICD shocks. She was treated with amiodarone and underwent an epicardial and endocardial ablation procedure of VT. Ablation was performed at the right ventricular epicardium and right ventricular outflow tract endocardium. After ablation, she continued to have episodes of VT requiring pace termination. A second epicardial and endocardial VT ablation procedure was performed. During that procedure, mapping was consistent with an intramyocardial circuit in the interventricular septum. Ablation was performed on the left and right
ventricular endocardial surfaces adjacent to the site at 40–50 W to try and achieve a deep septal lesion. Three months later, she developed slow VT that was consistent with recurrence from the same location and was treated with mexiletine and quinidine. She was evaluated for heart transplant at that time and was listed status 2B. Five months later, she again had recurrence of slow VT, which was initially controlled with increasing doses of mexiletine but recurred, causing palpitations and requiring pace termination. She underwent bilateral CSD and was discharged on postoperative day 1 without complications. One week later, an organ became available and she underwent cardiac transplant despite a lack of VAs recurrence.

All patients in our series underwent a minimally invasive thoracoscopic procedure and were discharged from the hospital on postoperative day 1 with no acute complications. Chest tube insertion was performed intraoperatively in 1 patient (14%) because of concern for pulmonary parenchymal injury; the chest tube was removed on postoperative day 1 without complications. One patient experienced changes in his sweating pattern (14%). No patients developed Horner syndrome.

Discussion
This series demonstrates that CSD can be an effective management strategy in patients with VA refractory to catheter ablation. In each case, catheter ablation was attempted or performed, but did not provide complete remission from VA. After modifying the sympathetic innervation to the substrate, a significant reduction in VA burden was achieved. In addition, these cases show that CSD is a safe, minimally invasive procedure with little associated morbidity. The excellent safety profile of this technique allows it to be used as an adjunct treatment to catheter ablation and medical therapy rather than something turned to in a time of desperation such as electrical storm. With continued improvements in technology and techniques, the role of catheter ablation in the management of patients with VA and ICD shocks is growing. However, there remains a significant portion of patients that develop recurrent VA despite catheter ablation or antiarrhythmic drug therapy, in many cases because of physiological or anatomical constraints. The advantage of CSD is that it overcomes many of these barriers, as it is not targeted to the heart directly.

With regard to the timing of CSD, sympathetic modulation has been found to be a useful therapy in the setting of VT storm by either a surgical or a percutaneous approach. We believe that autonomic modulation can play a crucial role in the management of patients with refractory VA before the development of electrical storm resulting from many different etiologies. Animal studies have demonstrated that myocardial ischemia can lead to remodeling of the stellate ganglia and increased sympathetic activity, supporting the idea that stellectomy in this setting may be protective. In addition, nuclear imaging with 123I-meta-iodobenzylguanidine (123I-MIBG), a radiolaabeled norepinephrine analog, can visualize cardiac sympathetic innervation and has been found to be abnormal in patients with both ischemic cardiomyopathy and nonischemic cardiomyopathy. Furthermore, integrating the data from 123I-MIBG scans into 3-dimensional electroanatomic maps from patients with ischemic cardiomyopathy, areas of sympathetic defects correlate with bipolar voltage-defined scar, and in cases where successful ablation was in an area of normal voltage, these sites correlated with a 123I-MIBG defect, highlighting the critical role of autonomic activity in the pathogenesis of VA.

Conclusion
Our series illustrates how sympathetic modulation may help to reduce VA in a wide spectrum of disease states refractory to catheter ablation. Further studies prospectively examining the efficacy of CSD in these settings should be pursued.

References


