



ORIGINAL RESEARCH

Arrhythmic Risk Profile and Outcomes of Patients Undergoing Cardiac Sympathetic Denervation for Recurrent Monomorphic Ventricular Tachycardia After Ablation

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BACKGROUND: Cardiac sympathetic denervation (CSD) has been used as a bailout strategy for refractory ventricular tachycardia (VT). Risk of VT recurrence in patients with scar-related monomorphic VT referred for CSD and the extent to which CSD can modify this risk is unknown. We aimed to quantify arrhythmia recurrence risk and impact of CSD in this population.

METHODS AND RESULTS: Adjusted competing risk time to event models were developed to adjust for risk of VT recurrence and sustained VT/implantable cardioverter–defibrillator shocks after VT ablation based on patient comorbidities at the time of VT ablation. Adjusted VT and implantable cardioverter–defibrillator shock recurrence rates were estimated for the subgroup who subsequently required CSD after ablation. The expected adjusted recurrence rates were then compared with the observed rates after CSD. Data from 381 patients with scar-mediated monomorphic VT who underwent VT ablation were analyzed, excluding patients with polymorphic VT. Sixty eight patients underwent CSD for recurrent VT. CSD reduced the expected adjusted VT recurrence rate by 36% (expected rate of 5.61 versus observed rate of 3.58 per 100 person-months, $P=0.01$) and the sustained VT/implantable cardioverter–defibrillator shock rates by 34% (expected rate of 4.34 versus observed 2.85 per 100 person-months, $P=0.03$). The median number of sustained VT/implantable cardioverter–defibrillator shocks in the year before versus the year after CSD was reduced by 90% (10 versus 1, $P<0.0001$).

CONCLUSIONS: Patients referred for CSD for refractory scar-mediated monomorphic VT are at a higher risk of VT recurrence after ablation as compared with those not requiring CSD, mostly because of their cardiac comorbidities. CSD significantly reduced both the expected risk of recurrences and VT burden.

Key Words: ablation ■ autonomic ■ cardiac sympathetic denervation ■ ventricular tachycardia

Implantable cardioverter–defibrillators (ICDs) reduce the risk of sudden cardiac death due to ventricular tachycardia (VT)/ventricular fibrillation (VF) in patients with reduced left ventricular ejection fraction (LVEF).¹ However, recurrent ICD shocks increase morbidity and mortality and decrease quality of life.² Therefore, catheter ablation has emerged as the leading strategy to reduce ICD shocks. Despite advances in ablation

strategy, however, a significant subset of patients continue to experience recurrent VT.

Cardiac sympathetic denervation (CSD) has been reported to reduce VT inducibility and ischemia-driven ventricular arrhythmias in animal models of myocardial infarction^{3,4} and decrease the burden of ICD shocks in patients with cardiomyopathy and recurrent VT/VF.⁵ However, given a heterogeneous population reported in

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study to quantify arrhythmia recurrence risk and impact of cardiac sympathetic denervation (CSD) exclusively in patients with scar-related monomorphic ventricular tachycardia (VT) referred for VT ablation and then CSD, excluding patients with any evidence of polymorphic VT.
- It demonstrates that patients undergoing CSD for refractory scar-mediated monomorphic VT are at a higher risk of VT recurrence after ablation as compared with those not referred for CSD, because of their underlying cardiac comorbidities.
- Nonetheless, CSD significantly reduced both the expected risk of ventricular arrhythmia recurrences and VT burden.

What Are the Clinical Implications?

- Despite the higher risk of VT recurrence in patients referred for CSD, this procedure can be an effective antiarrhythmic strategy for patients with ablation and drug refractory scar-related monomorphic VT.
- CSD is effective in reducing the burden of monomorphic VT in patients with ischemic as well as nonischemic cardiomyopathy.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
ATP	anti-tachycardia pacing
CSD	cardiac sympathetic denervation
MMVT	monomorphic ventricular tachycardia
NICM	nonischemic cardiomyopathy
NYHA	New York Heart Association
OHT	orthotopic heart transplantation
SHD	structural heart disease

previous case series, which included cardiomyopathy patients with VF, polymorphic VT, and monomorphic VT, controversy regarding the efficacy of CSD in the setting of scar-mediated monomorphic ventricular tachycardia (MMVT) exists. In addition, clinical trials comparing CSD with standard of care in patients with VT who have structural heart disease (SHD) are lacking. Therefore, the impact of CSD on VT recurrence rates over time is unknown.^{5,6} Retrospective case series have relied primarily on analysis of VT burden before versus after the procedure,⁵⁻¹⁰ and it is unknown what the rate of VT recurrence would have been in these patients, if CSD had not been performed, in

order to quantify the benefit of CSD. Finally, reported patients had many comorbidities, which were not accounted for in previous studies,⁵⁻¹⁰ and likely affected outcomes, making it difficult to delineate the efficacy of CSD. The purpose of this study was to quantify the impact of CSD on outcomes in patients with SHD and MMVT referred for catheter ablation, using a competing risk analysis to adjust for comorbidities.

METHODS

Data Collection

Retrospective data collection was approved by the UCLA institutional review board (#16-001417). The data that support the findings of this study are available from the corresponding author on reasonable request. Data from consecutive patients undergoing VT ablation for scar-mediated MMVT between 2007 and 2018 were analyzed. In the subgroup that required CSD, dynamic clinical data were also collected at the time of presentation for CSD. Notably, patients with any spontaneously occurring polymorphic VT, including those with both MMVT and polymorphic VT/VF, were excluded. Patients with MMVT who had polymorphic VT/VF induced with either invasive or noninvasive programmed electrical stimulation were still included in the study. Patients with focal monomorphic VT likely related to abnormal automaticity or triggered activity as well as those with bundle-branch reentrant VT were excluded from the study, independent of the presence of scar. SHD was defined by LVEF <50% or by presence of ventricular scar, hypertrophy, or inflammatory conditions. Presence of myocardial scar was identified with preprocedural imaging and confirmed with electroanatomical mapping, using standard endocardial and/or epicardial voltage criteria.¹¹ VT storm was defined as ≥ 3 sustained VT episodes or ICD therapies in 24 hours.

In patients with a history of multiple VT ablations, available data from the most recent (last) ablation procedure (referred to as the index VT ablation) at our center were used. The date of the index ablation procedure was used as the beginning of follow-up. In addition, the type of presentation at the time of index ablation was evaluated. Presentations were defined as: (1) elective: outpatient referral for ablation; (2) urgent: requiring hospitalization for VT/ICD shock(s) leading to referral for ablation during the same hospitalization; and (3) emergent: cardiocirculatory arrest and/or need for mechanical (including intra-aortic balloon pump, extracorporeal membrane oxygenation, or impella) support at the time of hospitalization for VT/ICD shock(s).

Electrophysiology Study and Ablation

Substrate-based ablation of scar guided by electroanatomic mapping was the primary strategy used in

all patients. If VT was induced and hemodynamically tolerated, activation and entrainment mapping were also performed in addition to substrate ablation to target appropriate ablation sites. Electroanatomic mapping was performed using CARTO (Biosense Webster) or NAVX (St. Jude Medical) with standard low-voltage settings (<1.5 mV) for border zone identification.¹² Substrate modification/ablation of scar containing areas with late activation or split, fractionated, or isolated late electrograms was performed in all patients.^{13–15} In addition, attempt at induction of VT was made with programmed ventricular stimulation using 2 drive cycle lengths, with up to 2 sites and 3 extrastimuli.

The clinical VT followed by nonclinical VTs were targeted for ablation. Pace mapping was used to target potential VT exit sites that matched the clinical VT in morphology, in patients who were inducible for VT.¹⁶ If VT was not inducible at the beginning of the case, then only substrate mapping and ablation were performed.

If percutaneous epicardial access could not be obtained because of prior cardiac surgery, the epicardium was accessed surgically. Catheter ablation was performed using open-irrigated catheters (ThermoCool, ThermoCool SF, or Navistar RMT [Biosense-Webster] or FlexAbility or FlexAbility Sensor-Enabled [Abbott]) or closed-loop irrigated catheters (Chilli, Boston Scientific).

Noninducibility of VT served as the desired procedural end point, and programmed stimulation was performed at the end of the procedure, unless prohibited by hemodynamic instability or procedural duration.¹¹ Epicardial mapping was performed in patients with epicardial scar noted on preprocedural imaging and/or an epicardial VT exit site suspected based on ECG morphology of VT or in patients with previously failed endocardial ablation.

Cardiac Sympathetic Denervation

CSD was performed via a minimally invasive (video- or robot-assisted) thoracoscopic surgical approach, as previously reported.^{5,17} Three 1.5-cm incisions were made in the ipsilateral chest wall under general anesthesia using single-lung inflation. After ipsilateral lung deflation, the sympathetic chain was identified behind the parietal pleura and dissected, and the lower one half to one third of the stellate ganglion as well as T2 to T4 thoracic ganglia were removed. In addition, when present, the nerve of Kuntz was divided.¹⁸ Histological confirmation of neuronal cell bodies within the ganglia was obtained via intraoperative frozen sections. Chest tubes were placed at the end of the procedure and removed within 24 hours of confirmation of lung re-expansion and lack of pleural effusion.

Follow-Up

Follow-up data were collected after the index ablation procedure. For the subgroup who required CSD after ablation, follow-up after ablation was censored at CSD. End points after ablation and after CSD included: (1) any appropriate ICD shock or sustained VT below ICD detection; and (2) any VT recurrence requiring ICD therapies, including anti-tachycardia pacing (ATP). Incidences of death and orthotopic heart transplantation (OHT) were also collected to evaluate competing risks. ICD interrogations and all clinical notes were carefully reviewed to confirm occurrence of ATP and appropriate ICD shocks. For patients followed at other institutions, referring cardiologists were contacted and/or electronic medical records accessing outside centers were used to obtain ICD interrogations and clinic notes. All clinical follow-up notes and ICD logs were reviewed to ensure that ICD shocks and therapies were appropriate and delivered for VT and not for supraventricular tachycardia. If any question regarding appropriateness or occurrence of ICD shocks or therapies was raised (ie, interrogation was uploaded without electrograms and/or clinical notes did not state whether the shock was appropriate), the patient and referring cardiologists were contacted by phone to obtain additional information.

Statistical Analysis

General Design

In this study, time zero was defined as the time of the last (index) ablation at our center. Only a nested subset of patients referred for VT ablation subsequently received CSD for arrhythmia recurrence. Since all eligible patients underwent ablation at time 0, a conventional parallel group analysis comparing 2 independent groups (those without CSD versus those with CSD) at time 0 was not feasible. Instead, the analytical approach used all of the patient data to create models relating key covariates/comorbidities to the outcome rates of VT recurrence, sustained VT/ICD shock, or mortality/transplant, and then used the data values in the CSD subset just before CSD to compute expected outcome rates for this subset's post-CSD follow-up (ie, the rates that would be expected if no CSD had been performed). This was compared with the actual observed outcome rates in the CSD population after their CSD.

Descriptive Variables

Continuous variables are presented as mean±SD or median (interquartile range [IQR]). Categorical variables are presented as counts/percentages. Significance of associations between variables was tested using

Student *t* or Mann-Whitney test for continuous and chi-square or Fisher exact test for categorical variables. $P \leq 0.05$ was considered statistically significant. Computations were performed using SAS 9.4 (SAS Institute Inc.) and R3.5.2 (R Project for Statistical Computing, www.r-project.org).

Multivariable Models

To compute the expected rate/risk of VT recurrence and sustained VT/ICD shocks after ablation adjusted for patient comorbidities, Fine-Gray competing risk models¹⁹ were developed using data at the time of presentation for VT ablation from all patients with scar-mediated MMVT. Predictors of VT recurrences were assessed using a Fine-Gray model to control for the competing risks of death and transplantation. Patient characteristics at the time of VT ablation were used for assessment of VT recurrence risk to reduce bias, because, at the time of referral for ablation, whether a patient would subsequently require CSD at follow-up was unknown (eg, a patient could die before undergoing CSD). Potential predictors assessed in the models were age, sex, New York Heart Association (NYHA) class, LVEF, urgency at presentation, VT storm, cardiomyopathy, chronic kidney disease, diabetes mellitus, and use of ≥ 2 antiarrhythmic drugs (AADs) before ablation. For VT recurrence, variables assessed also included acute ablation outcomes (ie, inducibility of clinical and nonclinical VTs at the end of the procedure), number of previous VT ablations, and presentation with ICD shock versus ATPs. Predictors of VT recurrence/ICD shocks were chosen based on physiological considerations, including previously published data on predictors of VT recurrence.^{20–22} Final models minimized the Akaike information criterion. Separate models were developed for all VT recurrences and sustained VT/ICD shocks. Cox proportional hazard models²³ were used to estimate risk of death and OHT. The proportional hazard assumption for the covariates were assessed via methods by Li, Scheike, and Zhang.²⁴

Model-based expected (adjusted) outcomes based on risk factors were compared with observed outcomes in patients with CSD. While values at the time of VT ablation were used to develop VT recurrence and death/OHT models, to determine the expected, adjusted event rates for outcomes in the subset of patients who underwent CSD, characteristics (covariate values) at the time just before CSD were used, given that for some of these variables (ie, NYHA class and LVEF) the value may have changed from the time of VT ablation. The *P* values were computed using a modified log-rank test.

Using these multivariable models and the data in the subset of patients who underwent CSD, expected rates (and corresponding hazard ratios [HRs]) for VT

recurrence and shocks after CSD were computed and compared with the observed VT recurrence rates and ICD shock rates (and corresponding HRs) after CSD, to quantify the impact of CSD on outcomes in this population (Data S1).

Impact of the Time of Index VT Ablation on Outcomes

Because of the relatively longer enrollment period (2007–2018), including the more recent routine use of contact-force catheters in the past 5 to 6 years, the time of the index VT ablation, before 2013 (2007–2012) versus after 2013 (2013–2018), was also specifically evaluated in the models as an additional covariate to determine any potential effect on outcomes.

RESULTS

Patient Characteristics

Between January 2007 and December 2018, 381 consecutive patients (aged 64 ± 13 years, 13% women, LVEF $32\% \pm 13\%$; 34% NYHA class III and 5% NYHA class IV; and 48% nonischemic cardiomyopathy [NICM]) underwent ablation for scar-mediated MMVT. During follow-up, 68 underwent CSD (12 had left CSD only). Median time from index VT ablation to CSD was 27 days (IQR, 6–114). The summarizes patient characteristics for the entire population ($n=381$) just before ablation, the group who received CSD after ablation because of recurrent VT ($n=68$), and the subgroup who did not receive CSD ($n=313$). The most frequent underlying NICM causes are also summarized in the Table. Remaining causes for NICM included alcoholic/drug-induced cardiomyopathy ($n=9$), familial dilated cardiomyopathy ($n=5$), rheumatic heart disease ($n=4$), left ventricular non-compaction ($n=2$), trauma ($n=2$), peripartum ($n=1$), chemotherapy-induced ($n=1$), and Birt-Hogg-Dube syndrome ($n=1$). Seven patients had mixed cardiomyopathy (cardiomyopathy out of proportion to the degree of coronary artery disease).

Compared with the overall population, those who were referred for CSD had a higher prevalence of NICM (78% versus 48%, $P < 0.01$), presented more frequently (at the time of ablation) with VT storm (72% versus 47%, $P < 0.01$) and ICD shocks (94% versus 84%, $P = 0.02$), and were more likely to have NICM caused by sarcoidosis/inflammatory causes (9% versus 3%, $P = 0.03$) or hypertrophic (9% versus 3%, $P = 0.02$) or valvular cardiomyopathy (7% versus 2%, $P = 0.02$) as compared with other NICM causes. They were also more likely to have had a history of VT ablation (median 1 [IQR, 0–2] versus 0 [IQR, 0–1], $P = 0.02$).

Table 1. Population Characteristics at the Time of Index VT Ablation

	Study Cohort Undergoing VT Ablation (n=381)	CSD Post-Ablation Attributable to VT Recurrence (n=68)	VT Ablation Without CSD (n=313)	P Value*	P Value†
Age, y	64±13	57±13	65±13	<0.01‡	<0.01‡
Women	48 (13)	8 (12)	40 (13)	0.85	0.82
Ischemic cardiomyopathy	189 (50)	12 (18)	177 (57)	<0.01‡	<0.01‡
Nonischemic cardiomyopathy	184 (48)	53 (78)	131 (42)	<0.01‡	<0.01‡
Idiopathic	76 (20)	21 (31)	55 (18)	0.04‡	0.01‡
ARVC	22 (6)	3 (4)	19 (6)	0.65	0.59
Myocarditis	12 (3)	4 (6)	8 (3)	0.26	0.15
Sarcoid/inflammatory	12 (3)	6 (9)	6 (2)	0.03‡	<0.01‡
Hypertrophic	11 (3)	6 (9)	5 (2)	0.02‡	<0.01‡
Valvular	8 (2)	5 (7)	3 (1)	0.02‡	<0.01‡
Chagas	11 (3)	4 (6)	7 (2)	0.20	0.10
Diabetes mellitus	111 (29)	17 (25)	94 (30)	0.49	0.41
Hypertension	241 (63)	43 (63)	198 (63)	1.00	1.00
Hyperlipemia	221 (58)	39 (57)	182 (58)	0.78	0.90
Atrial fibrillation	138 (36)	27 (40)	111 (35)	0.58	0.51
Prior VT ablation before the index	192 (50)	43 (63)	149 (48)	0.05	0.02‡
No. of prior VT ablations, median (IQR)	0 (0–1)	1 (0–2)	0 (0–1)	0.02‡	<0.01‡
Implantable device (none/ICD/CRT-D), n	24/233/124 (6, 61, 33)	1/44/23 (1, 65, 34)	23/189/101 (7, 60, 32)	0.28	0.19
LVAD	5 (1)	1 (1)	4 (1)	0.92	0.90
β-Blocker use	322 (85)	63 (93)	259 (83)	0.08	0.04‡
≥2 AAD use	96 (25)	23 (34)	73 (23)	0.14	0.07
Amiodarone use	215 (56)	41 (60)	174 (56)	0.55	0.48
VT storm	179 (47)	49 (72)	130 (42)	<0.01‡	<0.01‡
Prior ICD shock(s)	318 (84) 64 (94)		254 (81)	0.02‡	<0.01‡
NYHA class (I/II/III/IV), n	93/141/128/19 (24, 37, 34, 5)	10/29/28/1 (15, 43, 41, 1)	83/112/100/18 (26, 36, 32, 6)	0.14	0.06
Clinical presentation (elective/urgent/emergent), n§	108/261/9 (29, 68, 2)	18/46/3 (27, 68, 4)	90/215/6 (29/68/2)	0.61	0.45
LVEF (mean±SD)§	32±13	33±13	32±13	0.46	0.49
Chronic kidney disease (grade ≥3)¶	134 (35)	21 (31)	113 (36)	0.49	0.41
Preoperative ECMO/IABP/Impella	8 (2)	3 (4)	5 (2)	0.17	0.14

AAD indicates antiarrhythmic drug; ARVC, arrhythmogenic right ventricular cardiomyopathy; CRT-D, cardiac resynchronization therapy defibrillator; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; LVAD, left ventricular assist device; NICM, nonischemic cardiomyopathy; and NYHA, New York Heart Association.

*Comparison of the cardiac sympathetic denervation (CSD) subgroup to the overall study cohort.

†Comparison of the CSD subgroup to the group that did not undergo CSD (ventricular tachycardia [VT] ablation only). Values are expressed as mean±SD, number (percentage), or median (interquartile range).

‡Represent those for which comparisons were statistically significant at $P<0.05$.

§Data for clinical presentation were available for 378 of 381 patients and for left ventricular ejection fraction (LVEF) for 380 of 381 patients.

¶Estimated glomerular filtration rate <60 mL/min per 1.73 m².

The Table and Tables S1 and S2 summarize clinical and procedural characteristics at the time of VT ablation. Compared with the overall study population (n=381), patients who received CSD were more likely to have multiple (≥3) VT morphologies induced (62% versus 43%, $P=0.04$). At the end of the index ablation procedure, they were also more likely to be both

inducible for the clinical VT (14% versus 7%) and for the nonclinical VTs (25% versus 19%, $P=0.03$).

Ablation Outcomes

The median follow-up after the index VT ablation (n=381) was 15 months (IQR, 2–37 months). The median

follow-up was censored at CSD in those who underwent the procedure. Incidence of death/OHT and freedom from VT and sustained VT/ICD shocks are shown in Figure 1. After the index VT ablation and before CSD, VT recurred in 184 patients (48%), including sustained VT/ICD shocks in 153 patients (40%). VT and sustained VT/ICD shock recurrence was greater in the NICM population (57% and 46% for NICM versus 38% and 29% for ischemic cardiomyopathy, respectively; $P<0.01$).

After the index VT ablation and before CSD, 70 patients died (18%) and 23 underwent OHT (6%). Death ($n=36$) or OHT ($n=10$) occurred without VT recurrence in 46 patients. The median time to first VT recurrence, OHT, and death after the index VT ablation and before CSD was 0.5 months (IQR, 0–6), 6 months (IQR, 2–22), and 1.5 months (IQR, 0.5–10), respectively. The crude rate of death/OHT by the end of follow-up was 24% in those who did not experience VT recurrences, 39% in those who experienced VT recurrence but did not undergo CSD, and 49% in those who were referred for CSD for VT recurrence (Table S2).

Adjusted competing risk time to event models demonstrated that an advanced NYHA class, emergent indication, VT storm, and NICM were independently associated with VT recurrence after ablation, Figure 2A. Characteristics associated with recurrence of sustained VT/ICD shocks are shown in Figure 2B.

Cox multiple regression models using data at the time of index ablation identified advanced NYHA class, reduced LVEF, emergent indication for ablation, VT storm, chronic kidney disease, and an NICM cause as independently associated with death/OHT at follow-up (Figure S1). Importantly, outcomes (VT recurrence, ICD shocks, or death/OHT) were not influenced by the time period of the index VT ablation (between 2007–2013 versus 2013–2018) (Figures S2 and S3).

Indication for CSD

Indication for CSD in 78% of patients was recurrent sustained MMVT ($n=27$) or ICD shocks ($n=26$) after the last (index) ablation. The remaining patients received CSD for occurrence of multiple ATPs for clinical VT ($n=3$, 4%), frequent episodes of nonsustained VT matching the clinical VT ($n=2$, 3%), or inducibility of clinical VT despite their index ablation ($n=10$, 15%). The median time between the index VT ablation procedure and CSD was 27 days (IQR, 6–114) and 50% of patients ($n=34$) underwent CSD during the same admission as the index VT ablation. All patients had both the index VT ablation and CSD at the same center, and referral for CSD was consistent among patients. CSD was only performed if the patient was thought to have exhausted VT ablation as an option, ie, recurrence of

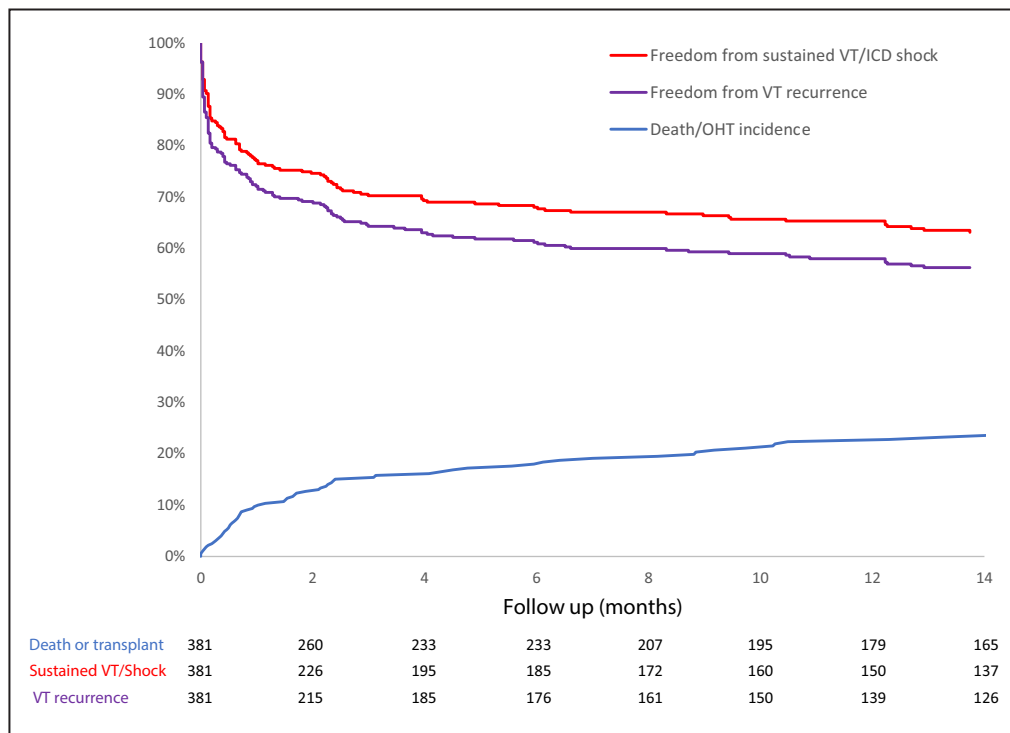


Figure 1. Freedom from all ventricular tachycardia (VT) recurrences and sustained VT/implantable cardioverter–defibrillator (ICD) shocks after ablation.

Freedom from all VT recurrences and from sustained VT/ICD shocks in the overall population (N=381) after the index VT ablation. The crude incidence of death and heart transplantation is also shown. OHT indicates orthotopic heart transplant.

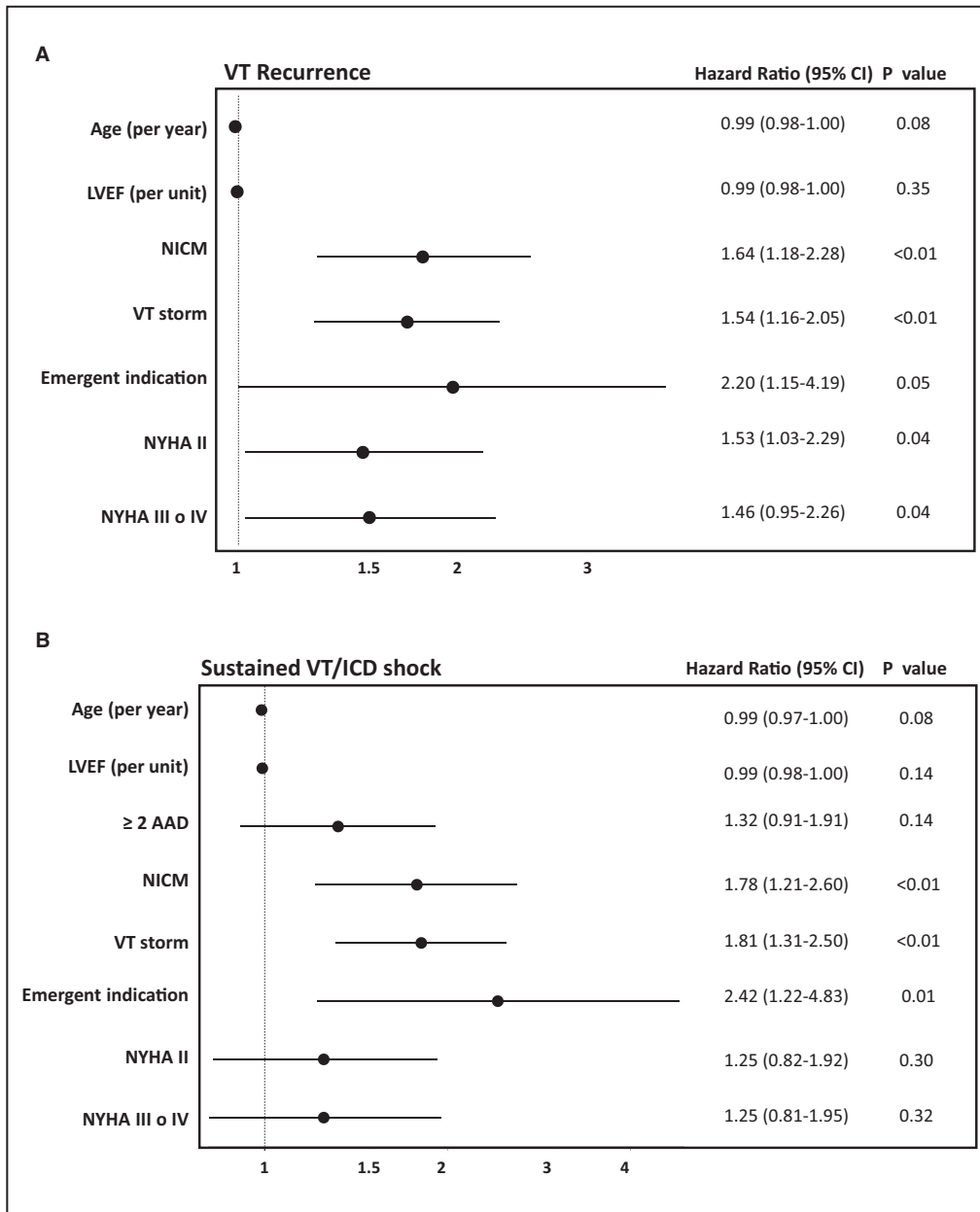


Figure 2. Predictors of ventricular tachycardia (VT) recurrences and sustained VT/implantable cardioverter–defibrillator (ICD) shocks after the index VT ablation.

Preprocedural characteristics associated with (A) VT recurrence (anti-tachycardia pacing and sustained VT/ICD shocks) and (B) sustained VT/ICD shocks alone after VT ablation in the overall population using the competing risk models are shown. AAD indicates antiarrhythmic drug; ICD, implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; and OHT, orthotopic heart transplantation.

arrhythmia despite both endocardial and epicardial (when indicated) mapping and ablation. This was particularly the case for patients who experienced multiple early recurrences during the same admission as the index VT ablation. Tables S1 and S2 demonstrate the procedural and clinical characteristics of the 68 patients who underwent CSD and those with VT

recurrences after VT ablation who were not referred for CSD. Patients referred for CSD were younger and were more likely to have NICM and a history of VT storm and ICD shocks. Nearly two thirds of patients referred for CSD had multiple (≥3) VT morphologies induced at the time of the index VT ablation. Finally, there was a higher prevalence of hypertrophic and valvular

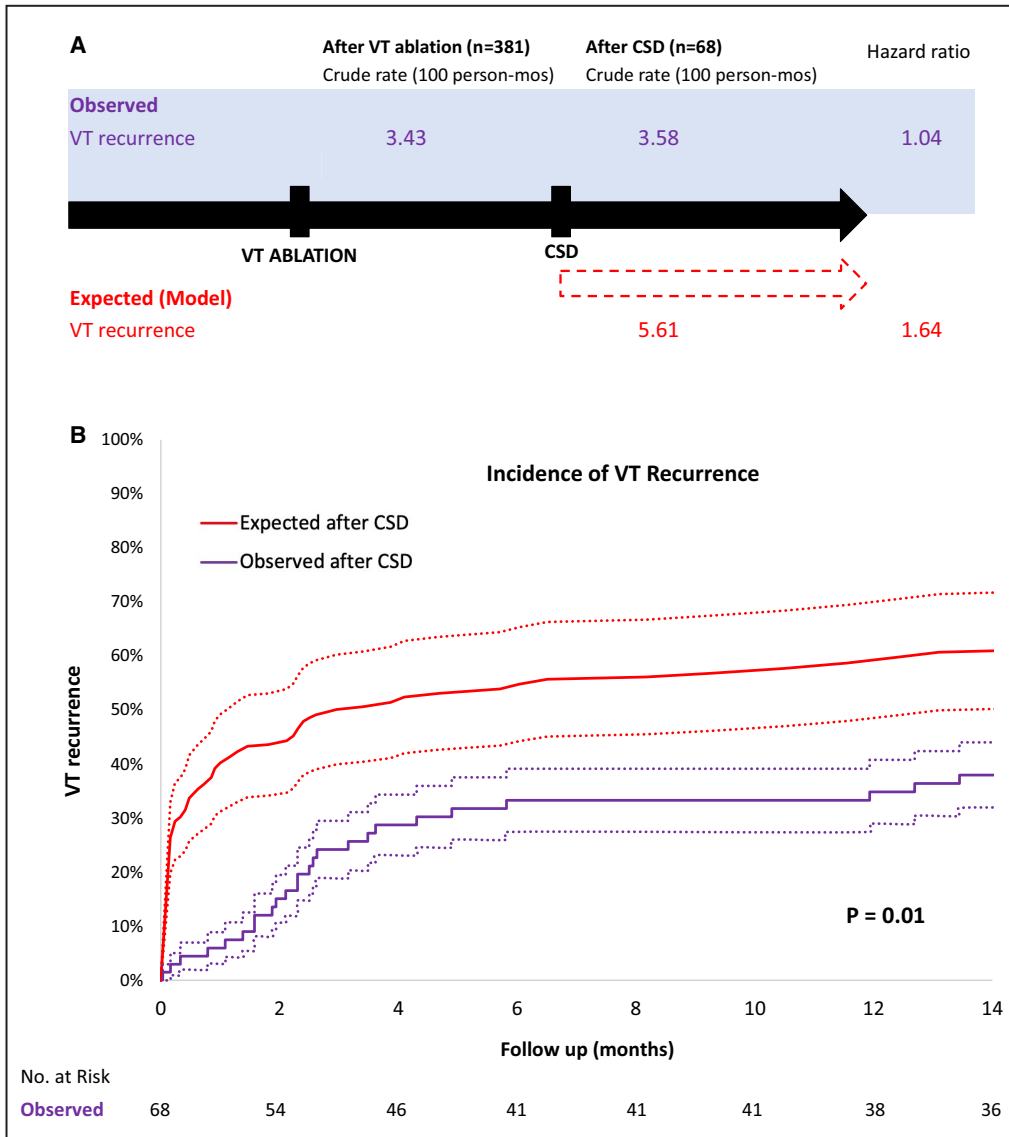


Figure 3. Comparison of expected vs observed rates of ventricular tachycardia (VT) recurrence after cardiac sympathetic denervation (CSD).

A, Observed: the crude rate of VT recurrences after VT ablation (3.43 per 100 person-months, n=381) and after CSD (3.58 per 100 person-months, n=68) are shown above the timeline (arrow). Expected: below the timeline (arrow), the expected recurrence rate for the subset of patients who underwent CSD (n=68), as estimated from the Fine-Gray model is shown (estimated as if they did not undergo CSD), adjusted for the greater comorbidities in this population. The expected rate of VT recurrences calculated from the model for the CSD population, adjusted for their comorbidities, was 5.61 per 100 person-months (shown below the timeline). Therefore, CSD reduced the expected recurrence rate from 5.61 to 3.58 per 100 person-months. The hazard ratio (HR) on top refers to the ratio between the crude rate of VT recurrences after CSD and the crude rate of VT recurrences after VT ablation, while the HR on the bottom refers to the expected ratio if the patients had not undergone CSD. Therefore, CSD led to a lower than expected HR. **B**, The adjusted expected vs observed cumulative VT recurrence risk rates are shown. CSD significantly reduced the observed vs expected HR for all VT recurrences by >30%. The observed curves account for the competing risk of death and orthotopic heart transplantation. Dashed lines represent the standard error of each curve.

cardiomyopathy and a shorter time to VT recurrence in the population referred for CSD.

Patient characteristics at the time of CSD versus the index ablation were not statistically different (Table S3).

Expected Versus Observed Outcomes in the CSD Group

Median follow-up after CSD was 17 months (IQR, 4-43 months). At 1 year, freedom from VT recurrence and sustained VT/ICD shocks was 65% and 73%,

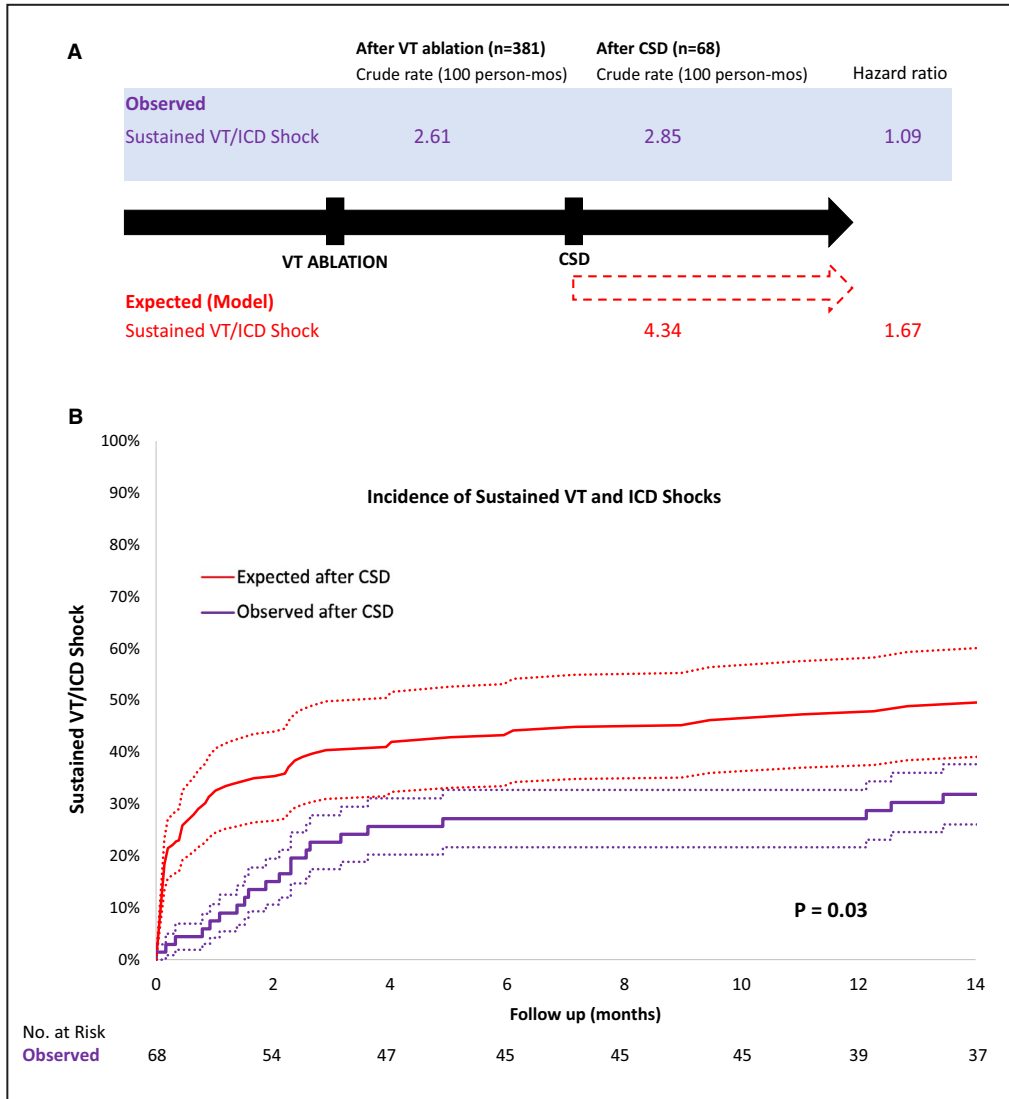


Figure 4. Comparison of expected vs observed rates of sustained ventricular tachycardia (VT)/implantable cardioverter-defibrillator (ICD) shocks after cardiac sympathetic denervation (CSD). **A**, Observed: the crude rate of sustained VT/ICD shocks after VT ablation (2.61 per 100 person-months, n=381) and after CSD (2.85 per 100 person-months, n=68) are shown above the timeline (arrow). Expected: below the time line (arrow) the model estimated expected adjusted sustained VT/ICD shocks recurrence rate for the subset of patients who underwent CSD (n=68) is shown, as if they had not undergone CSD. The expected rate of sustained VT/ICD shocks calculated from the model based on patient comorbidities was 4.34 per 100 person-months. The observed rate after CSD was reduced to 2.85 per 100 person-months. The hazard ratio (HR) above the arrow refers to the ratio between the crude rate of sustained VT/ICD shocks after CSD and the crude rate of sustained VT/ICD shocks after VT ablation, while the HR on the bottom of the arrow refers to the expected ratio if patients had not undergone CSD as estimated by the Fine-Gray model based on their greater comorbidities. Therefore, CSD led to a lower than expected HR. **B**, Expected and observed sustained VT/ICD shock cumulative risk curves over time after CSD are shown. The observed cumulative curves account for the competing risk of death/orthotopic heart transplantation. CSD significantly reduced the observed vs expected HR for sustained VT/ICD shocks. Dashed lines represent the standard error of each curve.

respectively, in the CSD group. At the end of follow-up, 19 patients died (28%) and 14 underwent OHT (21%). In 6 patients (9%), death (n=4) or OHT (n=2) occurred without VT recurrence.

Model-based expected VT recurrence rate adjusted for comorbidities in the CSD group was 5.61

per 100 person-months, while the actual observed post-CSD rate was 3.58 per 100 person-months. For sustained VT/ICD shocks, the expected hazard rate was 4.34, while the observed rate was 2.85 per 100 person-months. Therefore, CSD reduced expected rates for VT recurrence and ICD shocks by 36% and

34%, respectively. The expected HR for recurrent VT and sustained VT/ICD shocks, after adjusting for comorbidities, was 1.64 (95% CI, 1.40–1.91) and 1.67 (95% CI, 1.41–1.97), respectively (Figures 2A and 3A). Observed HRs after CSD were 1.04 and 1.09, respectively. In line with the above, therefore, CSD modified VT recurrence HRs by 36% (observed/expected HR, 0.64; 95% CI, 0.45–0.90 [$P=0.01$]) (Figure 3) and sustained VT/ICD shock HRs by 34% (observed/expected HR, 0.66; 95% CI, 0.45–0.96 [$P=0.03$]) (Figure 4). Expected versus observed HRs for death/OHT were not significantly different (observed/expected HR, 1.17; 95% CI, 0.74–1.86 [$P=0.49$]). Finally, major complications after CSD were observed in 5 patients (7%), including deep venous thromboembolism on postoperative day 2 ($n=1$), hemothorax ($n=1$) and pneumothorax ($n=1$), transient paralysis of the left phrenic nerve ($n=1$), and transient acute respiratory failure in the setting of severe amiodarone-induced lung toxicity ($n=1$). Minor complications/side effects of the procedure are detailed in Table S4.

ICD Shock and VT Burden in the CSD Population

The median number of sustained VT/ICD shocks in the 12 months before CSD was 10 (IQR, 5–18) versus 1 (IQR, 0–4) in the 12 months after follow-up (median reduction of 94%, $P<0.0001$) (Figure 5) and 2 (IQR 0–6) at last available follow-up (median of 17 months; IQR, 4–43 months [$P<0.0001$]). The median number of all VT episodes (sustained VT/ICD shocks/ATP) in the 12 months before CSD was 16.5 (IQR, 9–31) compared with 2 (IQR, 0–9) in the 12 months after follow-up (median reduction of 81%, $P<0.0001$) (Figure 6) and 4 (IQR, 1–12; $P<0.0001$ versus before CSD) at last available follow-up (median of 17 months; IQR, 4–43 months) after CSD. CSD reduced VT burden similarly in patients with ischemic cardiomyopathy versus those with NICM at 12 months (Figure 7). In the short period (median of 27 days) between the index VT ablation and CSD, the median number of VT episodes in patients referred for CSD was 5 (IQR, 1–12) and the median number sustained VT/ICD shocks was 4 (IQR, 1–7).

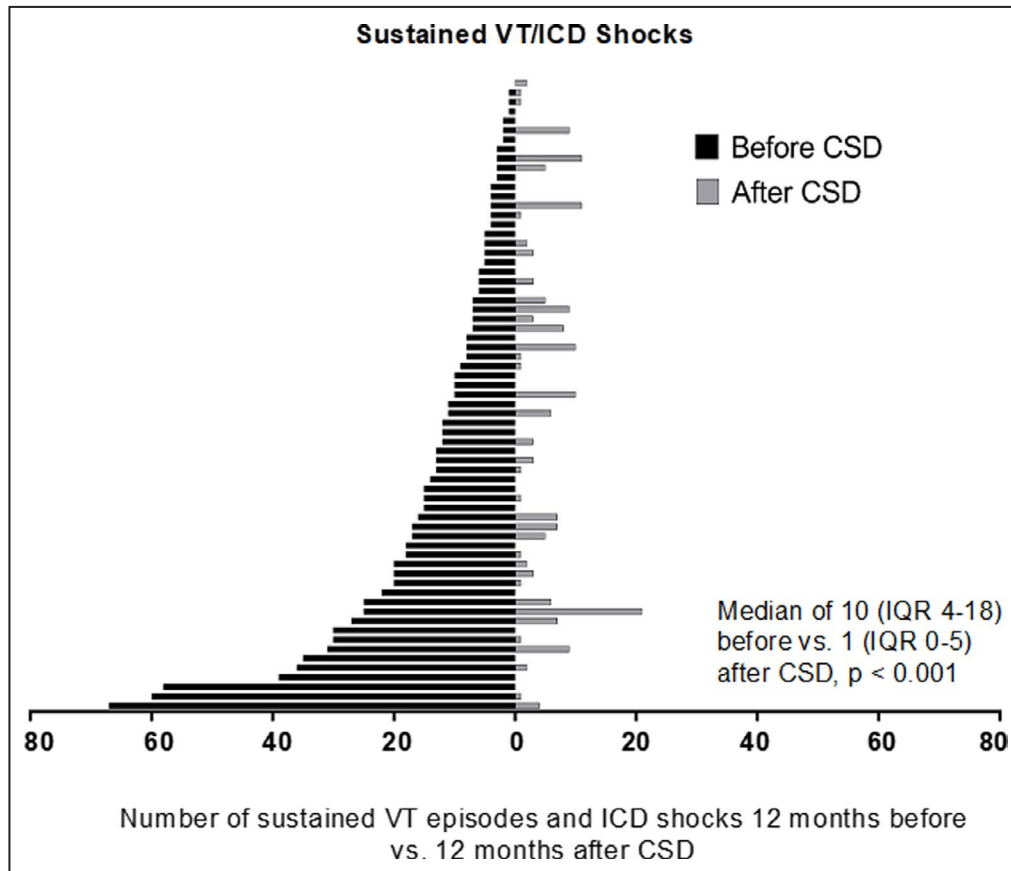


Figure 5. Sustained monomorphic ventricular tachycardia (VT)/implantable cardioverter-defibrillator (ICD) shocks 12 months before vs after cardiac sympathetic denervation (CSD). Number of sustained VT episodes and appropriate ICD shocks per person in the 12 months before vs the 12 months after CSD ($n=68$). The median number of sustained VT episodes and shocks was reduced from 10 (interquartile range [IQR], 4–18) to 1 (IQR, 0–5) ($P<0.001$).

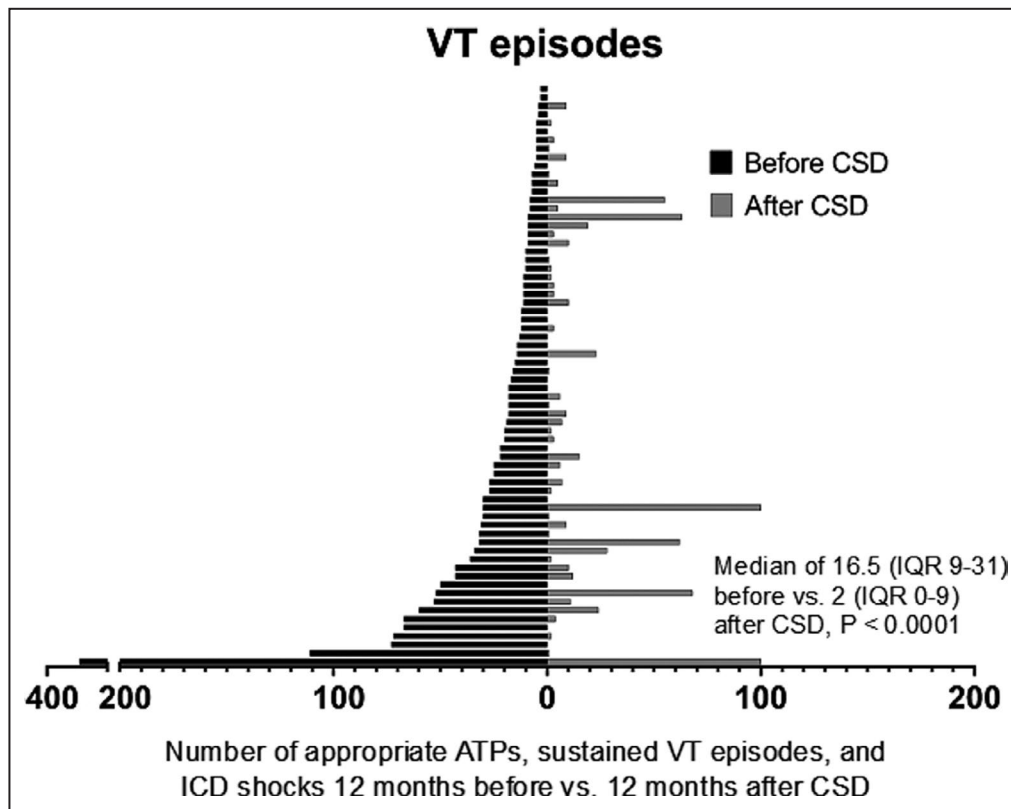


Figure 6. Monomorphic ventricular tachycardia (VT) episodes 12 months before vs after cardiac sympathetic denervation (CSD).

All VT episodes (including sustained VT/anti-tachycardia pacing (ATP)/implantable cardioverter-defibrillator [ICD] shocks) in the 12 months before CSD vs the 12 months after CSD. The median number of ATPs, sustained VT, and ICD shock episodes was significantly reduced in the 12 months after CSD as compared with the 12 months before CSD (from a median of 16.5 [interquartile range (IQR), 9–31 episodes] to a median of 2 [IQR, 0–9] episodes) ($P < 0.0001$).

Before CSD, 90% of patients were taking oral AADs (62% on amiodarone). At last available follow-up, 81% of patients were taking AADs (59% on amiodarone). The mean dosage of amiodarone per patient decreased from 391 ± 195 to 298 ± 197 mg ($P = 0.02$).

DISCUSSION

Major Findings

This study demonstrates that although patients with scar-mediated MMVT who subsequently require CSD after extensive and often multiple VT ablations were at higher risk of VT recurrence after ablation because of their baseline comorbidities, CSD significantly decreased the expected adjusted rates of VT recurrence and ICD shocks as well as VT burden. An emergent indication for ablation was an independent predictor of both mortality/OHT and VT recurrence, alluding to the importance of early referral for ablation and CSD.

A competing risk model was used in this study to estimate the relationship between patient factors and

VT recurrence risk in those with scar-mediated MMVT referred for ablation. This model was then utilized to estimate the expected risk of VT recurrence in patients referred for CSD, adjusting for their comorbidities. This adjusted risk was compared with the actual observed outcomes after CSD, to quantify the impact of the procedure.

Propensity score matching was not used in this study because of the inability to create a parallel design. All patients who underwent CSD also had a prior VT ablation, and nearly all patients had experienced a recurrence after VT ablation before receiving CSD. Therefore, a comparison of outcomes of patients with CSD only, adjusting for covariates, to those with VT ablation only was not appropriate. We also could not evaluate CSD as a covariate in a single Cox or Fine-Gray model for this same reason. All patients were at risk for death/transplantation, VT recurrence, and ICD shock, and these sometimes occurred before CSD. CSD was, in fact, given at least in part because of the deteriorating cardiovascular condition as indicated by arrhythmia recurrences before CSD, if the patient was

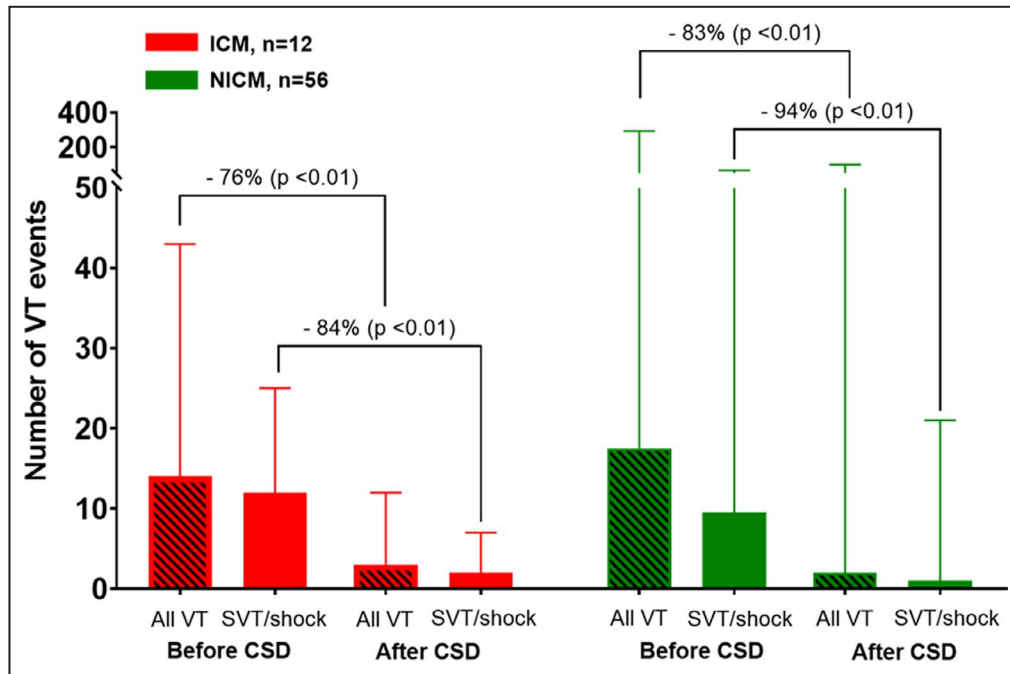


Figure 7. Ventricular tachycardia (VT) episodes 12 months before vs after cardiac sympathetic denervation (CSD) according to underlying type of cardiomyopathy.

VT episodes in the 12 months before as compared with the 12 months after CSD according to the underlying cardiomyopathy type. No difference was found when comparing the reduction for all VT episodes and sustained VT/implantable cardioverter-defibrillator shocks between patients with ischemic cardiomyopathy (ICM) and non-ICM (NICM). SVT indicates sustained VT episode.

alive and not transplanted. In addition, time-dependent covariates/characteristics such as LVEF, NYHA class, VT storm, and hemodynamic stability are dynamic and may change over time (ie, at presentation for VT ablation as compared with the presentation for CSD). We found that CSD reduced the risk of sustained VT/ICD shocks as well as all VT recurrences by >30% in patients with scar-mediated MMVT and a previous VT ablation, a novel finding of this study. To our knowledge, this is the first assessment of the value of CSD in this particular population, which is much more prevalent in clinical practice, than patients with polymorphic VT. The results quantify the expected benefits of CSD, which is critical in understanding the clinical impact of this procedure. Importantly, in this study CSD was not performed as an alternative to conventional redo VT ablation. Rather, CSD was performed as a bailout strategy in patients with a recent VT ablation (referred to as index) performed at our center, and patients were referred for CSD only if the referring physician expected that another VT ablation procedure would be futile, given findings of the most recent/index ablation.

Quantifying the Impact of CSD in MMVT

In previous case series of patients with SHD and refractory VT/VF who underwent CSD, including the largest series of 121 patients, 25% to 50% presented

with polymorphic VT or VF.⁵⁻¹⁰ Therefore, at least part of the benefit of CSD at follow-up was presumed to have been driven from the polymorphic VT population, and the effect of CSD in the setting of MMVT remained controversial. In this study, patients with any evidence of spontaneous polymorphic VT or idiopathic VF were excluded, in order to specifically assess the value of CSD in patients with scar-related MMVT.

In addition, in previous case series, patients undergoing CSD had significant comorbidities, which could have affected their outcomes and risk of VT recurrence after ablation.⁵⁻¹¹ Published studies have relied on comparing burden of ICD shocks before versus after CSD, without adjusting for comorbidities. Therefore, the true impact of CSD on VT recurrence over time remained unknown. Knowing this rate/risk is critical in physician and patient discussion of risks and expected procedural benefit. In this study, characteristics at the time of presentation for VT ablation were used to develop multivariable models, as at this time point, whether a patient would subsequently require CSD was unknown. While the models were developed to estimate rates of VT recurrence using data from all patients and values at the time of the index ablation, expected HRs for the CSD population were computed using values of covariates at the time of presentation for CSD, reflecting this group's

expected risk, while considering the dynamic nature of their disease. It is this adjusted rate and HR (calculated as if the 68 patients had not undergone CSD) that was compared with the observed rate and HR after CSD. This comparison demonstrated that CSD reduces the rate of sustained VT/ICD shocks by 34% and of all VT recurrences by 36%. Many of the factors associated with both VT recurrence and death/OHT in our model have also been validated in other studies,^{20–22,25,26} confirming that the models used in this study were robust in measuring risk and rates of outcomes after ablation.

Risk of VT Recurrence, ICD Shocks, Death, and OHT

In this study, patients who subsequently underwent CSD had more severe comorbidities, including a more advanced NYHA class, history of VT storm, and a higher number of previous ablations, even at the time of their index procedure. They were more likely to have causes of NICM associated with a greater risk of VT recurrence after ablation,²⁰ including HCM, sarcoidosis, and valvular heart disease. These subtypes of NICM often harbor a more challenging VT substrate, including intramural and epicardial scars, leading to the observed poorer outcomes after ablation compared with both ischemic cardiomyopathy and idiopathic dilated cardiomyopathy.²⁰ In line with other studies, this study shows that a higher NYHA class, use of ≥ 2 AADs, NICM, and VT storm are independently associated with risk of VT recurrence after ablation, resulting in the higher expected/adjusted risk of VT recurrence in the subgroup requiring CSD.^{20–22,25}

Type of admission (elective versus urgent/emergent) has been associated with increased in-hospital mortality and adverse events after VT ablation.²⁶ To the best of our knowledge, this is the first time an emergent indication is also recognized as an independent predictor of arrhythmia recurrence after VT ablation. Of note, the predictive value of an emergent indication was independent of NYHA functional class.

Management of Refractory MMVT

Catheter ablation reduces VT burden in patients with SHD.^{27,28} Despite significant technical progress, however, VT recurrence rates after ablation remain notable, especially in patients with NICM.^{20,25} Uptitration of AADs is of limited value because of toxicity and lack of efficacy often despite higher doses.^{28,29} This study demonstrates that in patients with scar-mediated MMVT, despite at least 1 (often extensive) VT ablation procedure, CSD provided additional benefit. In addition, the reduction in VT burden after CSD was

independent of the underlying type of cardiomyopathy (ischemic cardiomyopathy versus NICM).

Limitations

This is a single-center retrospective study representing outcomes at a tertiary referral center. ICD programming was left to the discretion of the treating physician and, therefore, was not uniform among patients. Although surgical techniques for CSD remained unchanged over the study period, VT ablation techniques may have evolved over time. In this cohort, however, a comparison of the first 5 versus the past 5 years of the study did not show a difference in outcomes. It should be recognized that the computed expected outcome rates assume that our models capture the essential comorbidity variables and covariates. Since this study consisted of only 68 patients with scar-mediated MMVT who underwent CSD, future validation is needed using a larger sample of patients.

CONCLUSIONS

This study demonstrates that patients with drug and ablation refractory scar-mediated MMVT who require CSD are at a higher risk of VT recurrence after ablation as compared with patients not referred for CSD, predominantly because of their higher prevalence of NICM and other comorbidities. In this population, CSD significantly decreased both the expected rates of arrhythmia recurrences and VT burden. An emergent indication for VT ablation is an independent predictor for both mortality/OHT and arrhythmia recurrence, alluding to the importance of early referral for ablation and CSD.

ARTICLE INFORMATION

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Disclosures

Drs Shivkumar, Ajjola, and Vaseghi have founder shares in NeuCures, Inc. UCLA has patents developed by Drs Vaseghi, Ajjola, and Shivkumar relating to cardiac neural diagnostics and therapeutics. The remaining authors have

no disclosures to report. The authors attest that they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent, where appropriate.

Supplementary Material

Data S1

Tables S1–S4

Figures S1–S3

REFERENCES

- Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;347:2253–2262.
- Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med*. 2008;360:1009–1017.
- Irie T, Yamakawa K, Hamon D, Nakamura K, Shivkumar K, Vaseghi M. Cardiac sympathetic innervation via the middle cervical and stellate ganglia and anti-arrhythmic mechanism of bilateral stellectomy. *Am J Physiol Heart Circ Physiol*. 2017;H392–H405.
- Schwartz PJ, Stone HL. Left stellectomy in the prevention of ventricular fibrillation caused by acute myocardial ischemia in conscious dogs with anterior myocardial infarction. *Circulation*. 1980;62:1256–1265.
- Vaseghi M, Barwad P, Malavassi Corrales FJ, Tandri H, Mathuria N, Shah R, Sorg JM, Gima J, Mandal K, Saenz Morales LC, et al. Cardiac sympathetic denervation for refractory ventricular arrhythmias. *J Am Coll Cardiol*. 2017;70:3070–3080.
- Vaseghi M, Gima J, Kanaan C, Ajjola OA, Marmureanu A, Mahajan A, Shivkumar K. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. *Heart Rhythm*. 2014;11:360–366.
- Cardona-Guarache R, Padala SK, Velazco-Davila L, Cassano A, Abbate A, Ellenbogen KA, Koneru JN. Stellate ganglion blockade and bilateral cardiac sympathetic denervation in patients with life-threatening ventricular arrhythmias. *J Cardiovasc Electrophysiol*. 2017;28:903–908.
- Richardson T, Lugo R, Saavedra P, Crossley G, Clair W, Shen S, Estrada JC, Montgomery J, Shoemaker MB, Ellis C, et al. Cardiac sympathectomy for the management of ventricular arrhythmias refractory to catheter ablation. *Heart Rhythm*. 2018;15:56–62.
- Saenz LC, Corrales FM, Bautista W, Traina M, Meymandi S, Rodriguez DA, Tellez LJ, Vaseghi M, Garcia F, Shivkumar K, et al. Cardiac sympathetic denervation for intractable ventricular arrhythmias in Chagas disease. *Heart Rhythm*. 2016;13:1388–1394.
- Cai C, Dai MY, Tian Y, Zhang P, Wittwer ED, Rho RH, Kapa S, McLeod CJ, Mulpuru SK, Lee HC, et al. Electrophysiologic effects and outcomes of sympatholysis in patients with recurrent ventricular arrhythmia and structural heart disease. *J Cardiovasc Electrophysiol*. 2019;30:1499–1507.
- Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, et al. 2019 HRS/EHRA/APHRS/LAHS expert consensus statement on catheter ablation of ventricular arrhythmias: Executive summary. *Heart Rhythm*. 2020;17: e155–e205. DOI: 10.1016/j.hrthm.2019.03.014.
- Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. *Circulation*. 2000;102:1288–1296.
- Arenal A, Glez-Torrecilla E, Ortiz M, Villacastin J, Fdez-Portales J, Sousa E, del Castillo S, Perez de Isla L, Jimenez J, Almendral J. Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease. *J Am Coll Cardiol*. 2003;41:81–92.
- Jaïs P, Maury P, Khairy P, Sacher F, Nault I, Komatsu Y, Hocini M, Forclaz A, Jadidi AS, Weerasoorya R, et al. Elimination of local abnormal ventricular activities: a new end point for substrate modification in patients with scar-related ventricular tachycardia. *Circulation*. 2012;126:2184–2196.
- Vergara P, Trevisi N, Ricco A, Petracca F, Baratto F, Cireddu M, Bisceglia C, Maccabelli G, Della BF. Late potentials abolition as an additional technique for reduction of arrhythmia recurrence in scar related ventricular tachycardia ablation. *J Cardiovasc Electrophysiol*. 2012;23:621–627.
- Stevenson WG, Sager PT, Natterson PD, Saxon LA, Middlekauff HR, Wiener I. Relation of pace mapping QRS configuration and conduction delay to ventricular tachycardia reentry circuits in human infarct scars. *J Am Coll Cardiol*. 1995;26:481–488.
- Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm*. 2009;8:752–759.
- Marhold F, Izay B, Zacherl J, Tschabitscher M, Neumayer C. Thoracoscopic and anatomic landmarks of Kuntz's nerve: implications for sympathetic surgery. *Ann Thorac Surg*. 2008;86:1653–1658.
- Collett D. *Modelling Survival Data in Medical Research*. 3rd ed. London, England: Chapman and Hall; 2015.
- Vaseghi M, Hu TY, Tung R, Vergara P, Frankel DS, Di Biase L, Tedrow UB, Gornbein JA, Yu R, Mathuria N, et al. Outcomes of catheter ablation of ventricular tachycardia based on etiology in nonischemic heart disease: an international ventricular tachycardia ablation center collaborative study. *JACC Clin Electrophysiol*. 2018;3:1141–1150.
- Santangeli P, Frankel DS, Tung R, Vaseghi M, Sauer WH, Tzou WS, Mathuria N, Nakahara S, Dickfeldt TM, Lakkireddy D, et al. Early mortality after catheter ablation of ventricular tachycardia in patients with structural heart disease. *J Am Coll Cardiol*. 2017;70:2105–2115.
- Vergara P, Tzou WS, Tung R, Brombin C, Nonis A, Vaseghi M, Frankel DS, Di Biase L, Tedrow U, Mathuria N, et al. Predictive score for identifying survival and recurrence risk profiles in patients undergoing ventricular tachycardia ablation. *Circ Arrhythm Electrophysiol*. 2018;12:e006730. DOI: 10.1161/CIRCEP.118.006730.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:466–475.
- Li J, Scheike TS, Zhang M. Checking fine and gray subdistribution hazard models with cumulative sums of residuals. *Lifetime Data Anal*. 2015;19:217–217.
- Kumar S, Romero J, Mehta NK, Fujii A, Kapur S, Baldinger SH, Barbhuiya CR, Koplak BA, John RM, Epstein LM, et al. Long-term outcomes after catheter ablation of ventricular tachycardia in patients with and without structural heart disease. *Heart Rhythm*. 2016;13:1957–1963.
- Katz DF, Turakhia MP, Sauer WH, Tzou WS, Heath RR, Zipse MM, Aleong RG, Varosy PD, Kao DP. Safety of ventricular tachycardia ablation in clinical practice: findings from 9699 hospital discharge records. *Circ Arrhythm Electrophysiol*. 2015;9:362–370.
- Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med*. 2007;257:2657–2665.
- Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, Thibault B, Rivard L, Gula L, Leong-Sit P, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *N Engl J Med*. 2016;374:1111–1121.
- Muser D, Hayashi T, Castro SA, Supple GE, Schaller RD, Santangeli P, Arkles J, Kumareswaran R, Nazarian S, Deo R, et al. Noninvasive programmed ventricular stimulation-guided management following ventricular tachycardia ablation. *JACC Clin Electrophysiol*. 2019;3:719–727.

SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Statistical Analysis

Observed VT rates: Total VT recurrences (including ATPs) and sustained VT/ICD shock rates after the index ablation and before CSD were determined as number of events divided by the total person-time at risk. Rates for these outcomes after CSD were determined similarly. *Observed* hazard ratio (HR) after CSD was calculated as the ratio between the actual post-CSD events rate (per 100 person/months) and the pre-CSD, post-ablation event rate (per 100 person/months).

The Fine-Gray competing risk model²¹ using variables from all subjects (n=381) was used to estimate rates of VT recurrences (including ATPs and sustained VT/ICD shocks) as well as sustained VT/ICD shocks alone before CSD, where death and transplantation were controlled for as a competing risk. Cox proportional hazard model²² using variables on all subjects at risk (n=381) at the time of the index VT ablation was used to model death/OHT rates before CSD. These models provided a (relative) risk score for VT recurrence and ICD shock outcomes in log hazard units. The antilog of the difference in risk score using values for covariates at the time of the CSD procedure minus values at the time of the index VT ablation resulted in the *expected* post-CSD to pre-CSD hazard ratio (HR). Values of the expected HRs to the observed HRs were compared to determine whether the expected post-CSD versus the observed post-CSD outcome rates were different, in order to quantify the impact of CSD on VT recurrence.

Missing data: Complete data on all variables for the 381 patients used in the study was available for analysis, with the exception of 4 patients (1%) that did not have LVEF and/or type of presentation documented at the time of VT ablation. For these variables, the available data from the 377 patients was used to determine hazard ratios in the multivariable models.

Table S1. Procedural Characteristics.

	Entire study Cohort (n=381)	CSD Post-ablation due to VT recurrence (n=68)	VT Ablation without CSD (n=313)	P value*	P value†	Recurrences but no CSD (n=116)	P value**
Epicardial access	192 (50)	38 (56)	154 (49)	0.68	0.32	64 (55)	0.92
Epicardial ablation	138 (36)	24 (35)	114 (36)	0.88	0.86	45 (39)	0.64
Number of VTs induced*							
- 0	51 (14)	8 (13)	43 (14)	0.04	<0.01	13 (11)	0.03
- 1	92 (25)	8 (13)	84 (13)			28 (24)	
- 2	66 (19)	7 (12)	59 (12)			27 (24)	
- ≥3	157 (43)	37 (62)	120 (38)			46 (40)	
VT ablation outcome ‡							
Non-inducible	211 (56)	24 (38)	187 (60)	0.03	<0.01	58 (50)	0.15
Non-inducible for clinical VT	71 (19)	16 (25)	55 (18)			22 (19)	
Inducible	25 (7)	9 (14)	16 (5)			7 (6)	
Not tested	68 (18)	14 (22)	55 (18)			29 (25)	
Intraoperative support (ECMO, IABP, Impella)	31 (8)	2 (3)	29 (9)	0.13	0.08	11 (9)	0.09
Complications	41 (11)	3 (4)	38 (12)	0.10	0.06	18 (2)	0.02

*Comparison of the CSD subgroup to the overall study cohort. †Comparison of CSD subgroup to the group that did not undergo CSD (had VT ablation only). **Comparison between those with recurrences after the index VT ablation who did (n=68) and did not (n=116) undergo CSD. Values are n (%). **Bold** values represent those for which comparisons were statistically significant at p value < 0.05. CSD = cardiac sympathetic denervation ECMO= extracorporeal membrane oxygenator; IABP = intra-aortic balloon pump; VT = ventricular tachycardia. ‡Number of induced VTs during the VT ablation procedure was available for 363 of 381 and for 60 of 68 patients, respectively, while data of VT inducibility at the end of the ablation procedure was available for 376 of 381 and for 63 of 68 patients.

TableS2. Patient Characteristics at Index VT ablation and Outcomes by VT Recurrence and CSD.

	CSD Post-ablation due to VT recurrence (n=68)	Recurrences but no CSD (n=116)	P value*	No recurrences after VT ablation (n=197)	P value†
Age (years)	57±13	64 ± 13	<0.01	66 ± 12	<0.01
Female	8 (12)	18 (16)	0.48	22 (11)	0.20
Ischemic cardiomyopathy	12 (18)	60 (52)	<0.01	117 (59)	<0.01
Nonischemic cardiomyopathy	53 (78)	54 (47)	<0.01	77 (39)	<0.01
- Idiopathic	21 (31)	26 (22)	0.20	29 (15)	<0.01
- ARVC	3 (4)	9 (8)	0.37	10 (5)	0.82
- Myocarditis	4 (6)	3 (3)	0.26	5 (2)	0.19
- Sarcoid/Inflammatory	6 (9)	3 (3)	0.06	3 (1)	<0.01
- Hypertrophic	6 (9)	0 (0)	<0.01	5 (2)	0.02
- Valvular	5 (7)	1 (1)	0.02	2 (1)	<0.01
- Chagas	4 (6)	2 (2)	0.12	5 (2)	0.19
Diabetes mellitus	17 (25)	34 (29)	0.53	60 (30)	0.39
Hypertension	43 (63)	71 (61)	0.78	111 (56)	0.32
Hyperlipemia	39 (57)	78 (67)	0.18	104 (53)	0.51
Atrial fibrillation	27 (40)	38 (33)	0.34	73 (37)	0.70
Prior VT ablation before the index	43 (63)	57 (49)	0.06	92 (47)	0.02
Number of prior VT ablations before index VT ablation (median, IQR)	1 (IQR 0-2)	0 (IQR 0-1)	0.79	0 (IQR 0-1)	<0.01
Implantable device (None, ICD, CRT-D)	1/44/23 (1, 65, 34)	10/80/26 (9, 69, 22)	0.05	13/109/75 (7, 55, 38)	0.17
LVAD	1 (1)	2 (2)	0.90	2 (1)	0.76
Beta-blocker use	63 (93)	99 (85)	0.14	160 (81)	0.26
≥ 2 AAD use	23 (34)	28 (24)	0.16	45 (23)	0.07
Amiodarone	41 (60)	63 (54)	0.43	111 (56)	0.57
VT Storm	49 (72)	52 (45)	<0.01	78 (40)	<0.01
Prior ICD shock(s)	64 (94)	97 (84)	0.04	157 (80)	<0.01
NYHA Class (I/II/III/IV)	10/29/28/1 (15, 43, 41, 1)	32/41/37/6 (28, 35, 32, 5)	0.10	51/71/63/12 (26, 36, 32, 6)	0.79
Clinical Presentation (Elective/urgent/emergent) ‡	18/46/3 (27, 68, 4)	34/78/3 (29, 68,3)	0.76	56/137/3 (29, 70, 1)	0.37
LVEF (mean±SD)‡	33 ± 13	31 ± 13	0.23	33 ± 13	0.66
CKD (Grade ≥3) §	21 (31)	34 (29)	0.82	80 (41)	0.15
Pre-operative ECMO/IABP/Impella	3 (4)	0 (0)	0.09	5 (2)	0.43
Time from index VT ablation to first recurrence, days (median, IQR)	4 (1-39)	39 (5-490)	<0.01		
Death/OHT by the end of FU	33 (49)	45 (39)	0.19	48 (24)	<0.01
Time from index VT ablation to death/OHT, days (median, IQR)	204 (102-795)	49 (16-369)	<0.01	171 (21-442)	0.11

* Comparison between those with recurrences after the index VT ablation who did (n=68) and did not (n=116) undergo CSD. †Comparison of the CSD subgroup (n=68) to the subgroup who did not suffered recurrences after the index VT ablation (n=197). Values are mean ± SD, n (%), or median (interquartile range). **Bold** values represent those for which comparisons were statistically significant at p value < 0.05. AAD = antiarrhythmic drugs; ARVC = arrhythmogenic right ventricular cardiomyopathy CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; CSD = cardiac

sympathetic denervation; ECMO = extracorporeal membrane oxygenator; IABP= intra-aortic balloon pump; ICD = Implantable cardioverter-defibrillator; ICM = ischemic cardiomyopathy; LCSD = left cardiac sympathetic denervation; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction, NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; OHT = orthotopic heart transplant. VT = ventricular tachycardia. †Data about clinical presentation was available for 378 of 381 patients and about LVEF for 380 of 381 patients. § eGFR <60 ml/min/mq.

Table S3. Characteristics at the Time of VT Ablation vs. CSD.

Covariate	At VT ablation n=68	At-CSD n=68
Age	57 ±13	57±13
LVEF	33±13	34±12
VT storm	49 (72)	52 (76)
CKD	21 (31)	25 (36)
≥ 2 AAD use	23 (33)	23 (33)
NYHA Class		
NYHA Class I	10 (15)	8 (12)
NYHA Class II	29 (43)	33 (49)
NYHA Class III	28 (41)	23 (33)
NYHA Class IV	1 (1)	4 (6)
Elective indication	18 (27)	17 (25)
Urgent indication	46 (68)	48 (71)
Emergent indication	3 (4)	3 (4)

Values are mean ± SD, n (%), or median (interquartile range). AAD = antiarrhythmic drugs; CKD = chronic kidney disease; CSD = cardiac sympathetic denervation; LVEF = left ventricular ejection fraction; NICM= nonischemic cardiomyopathy; NYHA = New York Heart Association; VT = ventricular tachycardia.

Table S4. Minor complications after CSD.

Type of complication	Number of patients, (%)	Management
Ptosis - Transient * - Not transient	5 (7) 4 (6) 1 (1)	No specific treatment
Abnormal skin sensitivity/neuropathic pain - Transient * - Not transient	25 (37) 21 (31) 4 (6)	Gabapentin and pregabalin as needed
Compensatory hyperhidrosis	7 (10)	No specific treatment

*Transient = completely resolved within 3 months after CSD.

Figure S1. Pre-procedural characteristics found to be independently associated with death/orthotopic heart transplantation (OHT) in the overall study cohort (n=381).

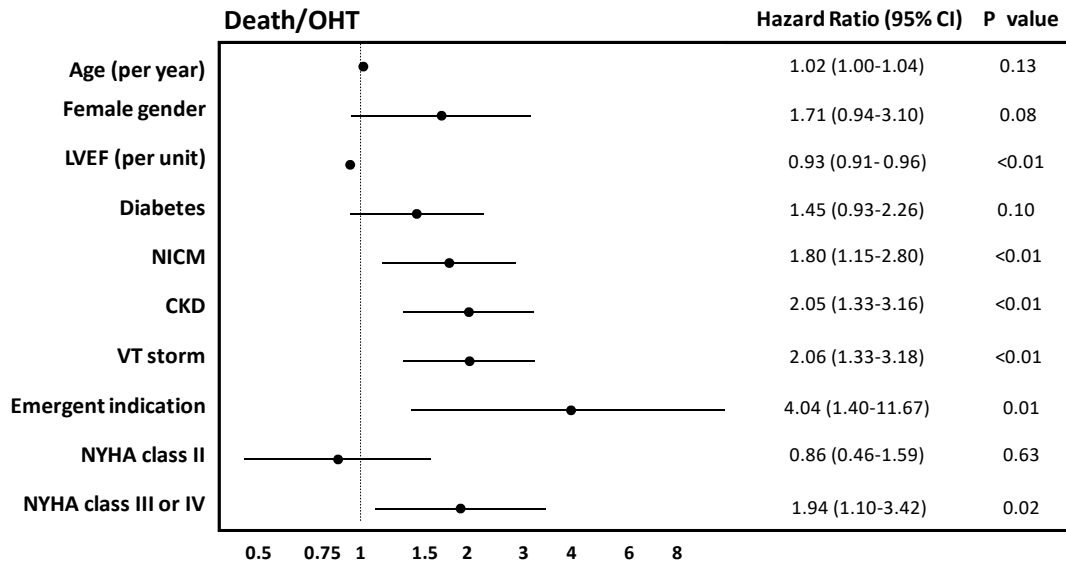
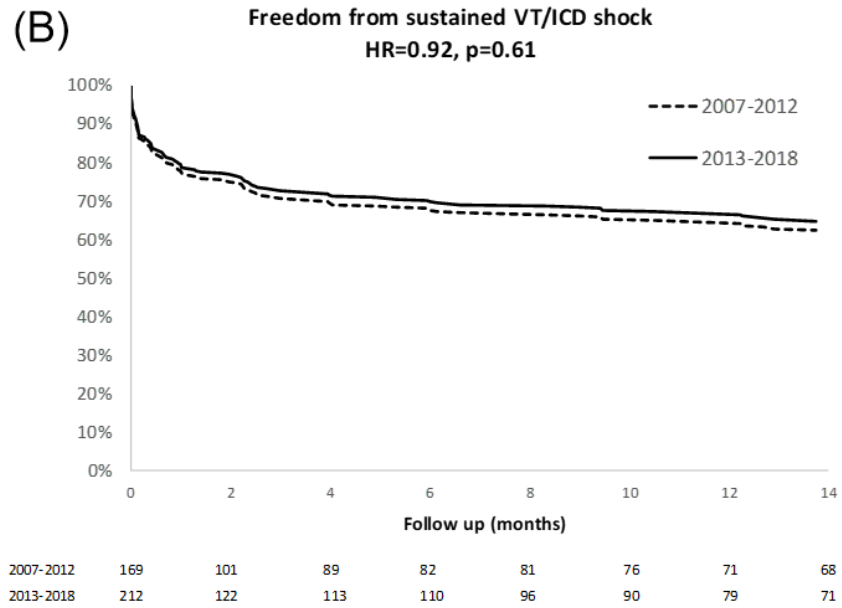
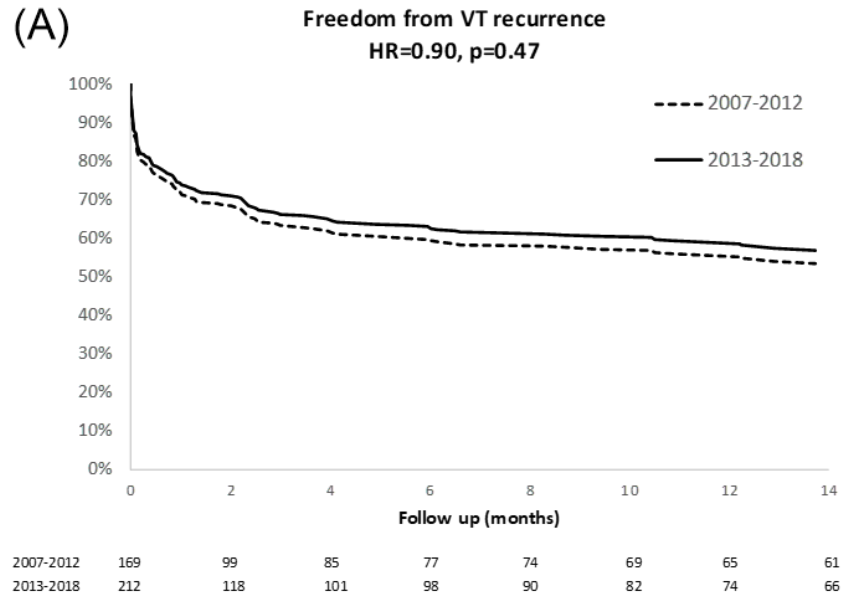
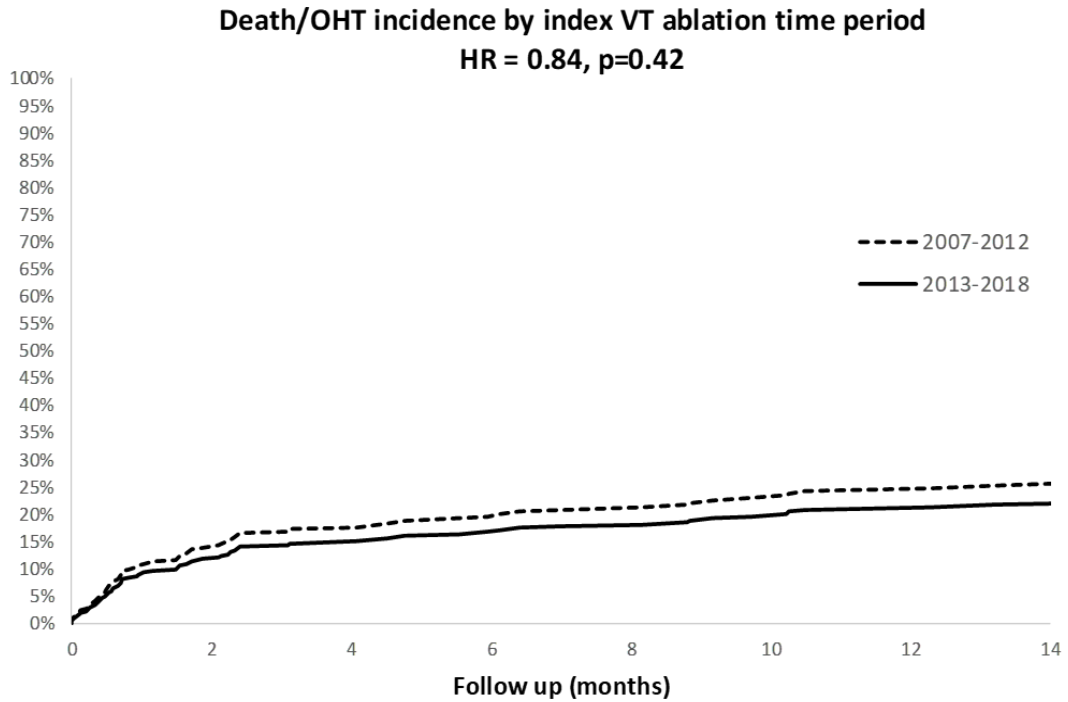


Figure S2. Freedom from VT recurrence (panel A) and from sustained VT/ICD shock (panel B) by index VT ablation time period (2007 to 2012 vs. 2013-2018).



Hazard ratios by index VT ablation time periods are adjusted for covariates.

Figure S3. Incidence of death/OHT (orthotopic heart transplant) by index VT ablation time period (2007 to 2012 vs. 2013 to 2018).



2007-2012	169	125	111	105	99	94	92	82
2013-2018	212	138	125	116	113	106	95	91

Hazard ratio by index VT ablation time periods is adjusted for covariates.