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ORIGINAL RESEARCH

Trigger Type and Breakthrough Cardiac Events in Inherited Arrhythmia Syndromes After Left Cardiac Sympathetic Denervation

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ABSTRACT

BACKGROUND Left cardiac sympathetic denervation (LCSD) confers a strong antifibrillatory effect and provides significant therapeutic efficacy for patients with genetic heart diseases, especially long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). We hypothesize that LCSD's efficacy may differ among patients experiencing adrenergic (AD) vs nonadrenergic (non-AD) triggered symptoms before LCSD.

OBJECTIVE In this study, we sought to evaluate the association between AD and non-AD triggered events and the subsequent risk of breakthrough cardiac events (BCEs) after LCSD.

METHODS A retrospective review of all previously symptomatic patients with either LQTS or CPVT who underwent LCSD at our institution since 2005 was performed. Data from electronic medical records was abstracted for cardiac event (CE) trigger type (AD or non-AD) before and after LCSD. CEs and BCEs were defined as arrhythmogenic syncope, seizure, appropriate ventricular fibrillation–terminating therapies, and sudden cardiac arrest or death.

RESULTS Among 154 pre-LCSD symptomatic patients (mean age at diagnosis: 15 ± 12 years; follow-up after LCSD: 5.9 ± 4.2 years) with LQTS (n = 105; 68%) or CPVT (n = 49; 32%), 49 patients (32%) had >1 BCE. Post-LCSD BCEs were significantly higher in patients with non-AD triggered CE (n = 30/56; 54%)) compared with patients with AD-triggered CE (n = 19/98; 19%; $P < 0.0001$). The subset analysis found fewest BCEs in LQT1 patients with AD triggers (OR: 0.24, $P < 0.0001$). To date, no BCEs have occurred in LQT2, LQT3, or LQT Minor patients with pre-LCSD AD-triggered CEs.

CONCLUSIONS There is a marked pre-LCSD phenotypic determinant of LCSD's therapeutic efficacy. Independently from underlying genotype, patients with adrenergic triggers associated with their pre-LCSD symptoms had a greater reduction in disease-mediated BCEs. (JACC Clin Electrophysiol. 2026;■:■–■) © 2026 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AD = adrenergic

BCE = breakthrough cardiac event

CE = cardiac event

CPVT = catecholaminergic polymorphic ventricular tachycardia

LCSD = left cardiac sympathetic denervation

LQTS = long QT syndrome

Long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are inherited cardiac channelopathies that predispose individuals to life-threatening arrhythmias.[1,2] Though not all events are adrenergic-mediated, sympathetic stimulation plays a central role in triggering arrhythmias in many patients, particularly in CPVT and specific LQTS genotypes, such as LQT1, 3, and 4.[3,4] These episodes often occur during physical or emotional stress and can lead to syncope, torsades de pointes, or sudden cardiac arrest.[5,6]

Despite the common use of beta-blockers in both diseases to blunt the systemic response to adrenergic stimulation, a subset of patients remains at high risk for recurrent cardiac events (CEs).[7] Left cardiac sympathetic denervation (LCSD) is a surgical intervention that has become an important therapeutic strategy to manage patients who are refractory to conventional therapies or need additional protection based on clinical risk stratification.[8,9]

Although LCSD is associated with a significant reduction in CEs in both LQTS and CPVT as an associate therapy or monotherapy, patient outcomes and recurrence of CEs vary widely.[10] This heterogeneity raises the question of whether the nature of the pre-LCSD arrhythmic trigger, adrenergic (AD) vs non-adrenergic (non-AD), influences the magnitude of benefit conferred by the procedure. Therefore, we evaluated the post-LCSD outcomes of patients with LQTS and CPVT based on the pre-LCSD CE trigger type with the goal of further informing the expected therapeutic efficacy of LCSD to guide patient selection and advance individualized care in inherited arrhythmia syndromes.

METHODS

This study involved a retrospective review of all patients diagnosed with either LQTS or CPVT at the Windland Smith Rice Genetic Heart Rhythm Clinic (Mayo Clinic, Rochester, Minnesota), who underwent LCSD from 2005 to 2024. Patients were included if they 1) had experienced >1 CE before LCSD ("symptomatic") and 2) had a minimum of 1 year of follow-up data available after LCSD. The primary objective was to compare the patients with AD- and non-AD-triggered events before LCSD and evaluate trigger-associated clinical outcomes after the procedure.

STUDY POPULATION AND DATA COLLECTION. Data were abstracted from electronic medical records, including patient demographics, clinical characteristics, cardiologic evaluations, genetic test results, electrocardiography records, trigger type (AD vs non-AD), CEs before LCSD, and breakthrough cardiac events (BCEs) after LCSD.

DEFINITION OF CARDIAC EVENTS AND TRIGGER TYPE. CEs (and BCEs) were defined as arrhythmogenic syncope, seizure, appropriate ventricular fibrillation-terminating therapies, documented sustained ventricular arrhythmias, sudden cardiac arrest, and sudden cardiac death. The trigger for each CE before LCSD was classified as either AD, including exercise, early recovery from exercise, physical or emotional stress, and, in the case of LQT2, auditory stimuli, or non-AD, which included rest and sleep. The classification was based on clinical documentation and patient or family recall of the event and followed definitions from a previous study.[11]

OPERATIVE TECHNIQUE. The surgical denervation procedure was performed as previously described.[12] Briefly, the left sympathetic ganglia are exposed and isolated with the use of a video-assisted transthoracic approach. The sympathectomy encompasses an en-bloc resection of the lower half of the stellate ganglion (T1), as well as T2 through T4 segments of the sympathetic chain, achieved by dividing the major rami communicans and branches projecting to the left ventricle. Following completion of the procedure, all patients are monitored overnight with continuous cardiac monitoring. Over 95% of the patients are discharged on the day after their LCSD.

STATISTICAL ANALYSIS. Descriptive statistics summarized cohort characteristics (mean ± SD and n [%]). Univariable logistic regression was used to estimate associations between AD vs non-AD triggers and post-LCSD events in the total cohort, as well as in subgroups of CPVT, LQTS, and LQTS genotypes (LQT1, LQT2, LQT3, and LQT Minor). As a secondary analysis, a multivariable model was fitted in the LQTS cohort, adjusting for baseline QTc per 10 ms. Results are reported as ORs with 95% CIs. Within non-AD patients, pre- vs post-LCSD event counts were shown as spaghetti plots and compared with the use of 2-sided Wilcoxon signed rank tests. Analyses were performed with the use of RStudio (2024.09.0+375) and Prism GraphPad (10.03.01); $\alpha = 0.05$.

ETHICAL CONSIDERATIONS. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board. Owing to its retrospective nature, informed consent was waived, and all patient data was anonymized to protect confidentiality.

RESULTS

COHORT CHARACTERISTICS. Overall, 385 patients evaluated for LQTS or CPVT at Windland Smith Rice Genetic Heart Rhythm Clinic underwent LCSD from 2005 to 2024. Of these, 299 patients (77%) were diagnosed with LQTS and 86 with CPVT (22%). The cohort development for this study is outlined in Figure 1.

BASELINE CHARACTERISTICS. After excluding asymptomatic patients and those lacking sufficient follow-up, our study cohort consisted of 154 previously symptomatic patients, including 105 with LQTS (68%) and 49 with CPVT (32%) (Figure 1). The mean age at diagnosis was 15 ± 12 years (LQTS: 14 ± 13 years; CPVT: 16 ± 9 years), and the mean age at LCSD was 19 ± 12 years (LQTS:: 19 ± 13; CPVT: 20 ± 10 years). Overall, 53% of the cohort was female, and the mean follow-up time after LCSD was 5.9 ± 4.2 years. The clinical characteristics of the study cohort, as well as details specific to LQTS and CPVT, are summarized in Table 1.

Before LCSD, 104 of the 154 patients (67%) were on a single medication and 50 (33%) required a combination of pharmacologic treatments. Usage patterns differed between LQTS and CPVT patients, as summarized in Table 1. Overall, 139 of the 154 patients (90%) were on beta-blocker therapy, with nadolol being the most frequently used (CPVT: 93%); LQTS: 88%)). Nearly half of the patients (71; 46%) had an implantable cardioverter-defibrillator, with similar rates in LQTS (44%) and CPVT (48%).

Before LCSD, 98 of the 154 patients (63%) experienced >1 AD-triggered CE. The distribution of triggers reflected disease mechanisms: AD triggers occurred in 54 (51%) of the 105 LQTS and 44 (89%) of the 49 CPVT patients (Table 2). To show differences in severity of events and triggers before LCSD, breakdowns by event type (eg, survived cardiac arrest, syncope) are provided in Supplemental Tables 1 and 2.

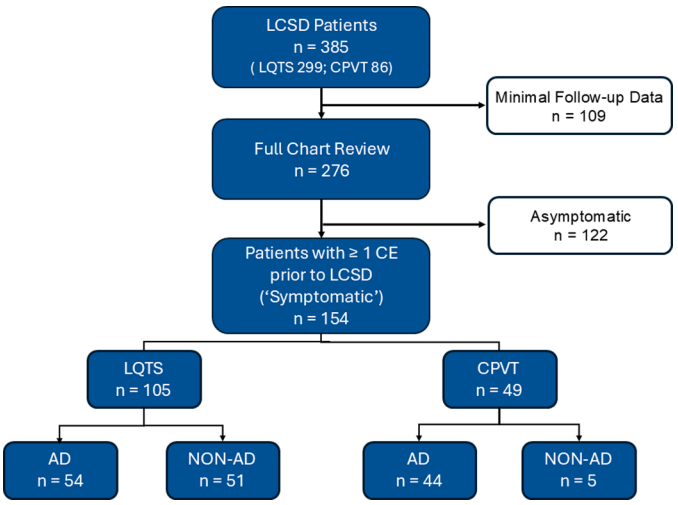
Within LQTS, AD triggers were predominant in LQT1 (47/63; 75%), whereas non-AD triggers were more common in LQT2 (20/26; 77%), LQT3 (9/10; 90%), and LQT Minor (7/10; 70%) (Table 3).

In LQT1 (n = 63), 47 patients had AD triggers—all exercise-related—with swimming being the most common activity (n = 18). Four of these events occurred during the short or early recovery phase. The remaining 16 patients had non-AD triggers, of which 2 occurred during sleep (1 in the postpartum setting and 1 after alcohol intoxication).

In LQT2 (n = 26), 6 patients had AD triggers, including 4 events on awakening with an alarm and 2 events during exercise. The 20 patients with non-AD triggers included 2 sleep-related events not associated with alarm or arousal.

In LQT3 (n = 10), AD triggers were rare, with only 1 patient falling into this category. The majority (n = 9) had non-AD triggers, including 3 with sleep-related

FIGURE 1 Flowchart of Cohort Identification



The process of study cohort identification, detailing patient selection, inclusion and exclusion criteria application, and stratification into LQTS and CPVT cohorts split by AD- and non-AD-triggered CEs. AD = adrenergic; CE = cardiac event; CPVT = catecholaminergic polymorphic ventricular tachycardia; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome; non-AD = nonadrenergic.

TABLE 1 Clinical Characteristics of Symptomatic LCSD Cohort

	Total Cohort	LQTS	CPVT
Cohort	154	105	49
Age at diagnosis, y	15 ± 12	14 ± 13	16 ± 9
Age at LCSD, y	19 ± 12	19 ± 13	20 ± 10
Sex, female	82 (53)	60 (57)	22 (45)
Family history of SCA <45 years old	53 (34)	36 (34)	17 (34)
Follow-up time after LCSD, y	5.9 ± 4.2	5.9 ± 4.3	5.9 ± 3.8
Treatment modalities before LCSD			
Treatment combinations			
Patients on 1 treatment	104 (67)	84 (80)	20 (41)
Patients on >1 treatment	50 (33)	21 (20)	29 (59)
Pharmacologic treatment			
Beta-blocker, nadolol	102 (66)	65 (62)	37 (75)
Beta-blockers, other	37 (24)	28 (26)	9 (18)
Flecainide	29 (18)	3 (3)	26 (53)
Mexiletine	22 (14)	21 (20)	1 (2)
Implantable cardioverter-defibrillator	71 (46)	47 (44)	24 (48)

Values are presented as mean ± SD or n (%).
CPVT = catecholaminergic polymorphic ventricular tachycardia; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome.

TABLE 2 Impact of Pre-LCSD Trigger Type on Post-LCSD Cardiac Events

	Pre-LCSD Trigger Type	Post-LCSD BCE	No post-LCSD BCE	OR (95% CI)	*P* Value
Total Cohort (n = 154)	AD 98 (63)	19 (19)	79 (81)	0.21 (0.09-0.42)	<0.0001
	Non-AD 56 (37)	30 (54)	26 (46)		
LQTS (n = 105)	AD 54 (51)	9 (17)	45 (83)	0.14 (0.05-0.36)	<0.0001
	Non-AD 51 (49)	30 (59)	21 (41)		
CPVT (n = 49)	AD 44 (89)	10 (23)	34 (77)	∞ (NA)	0.57
	Non-AD 5 (11)	0 (0)	5 (100)		

Values are presented as n (%). Percentages represent the proportion of patients with AD triggers relative to total patients in each cohort. ORs were calculated based on the formula (events A/nonevents A)/(events B/nonevents B). ∞ indicates an infinite OR owing to the absence of events in the non-AD group (non-AD). *P* values were derived by means of Fisher test.

BCE = breakthrough cardiac event; CPVT = catecholaminergic polymorphic ventricular tachycardia; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome.

events not linked to alarm or arousal. Recurrence after LCSD was frequent in this genotype, with 8 of 10 patients experiencing events; the only patients without recurrence were 1 with an AD exercise trigger and 1 with a non-AD event during sleep before LCSD.

POST-LCSD BCEs. Overall, 49 of the 154 patients (32%) experienced >1 BCE after LCSD during an average follow-up of nearly 6 years. Patients with AD-triggered pre-LCSD CEs had significantly fewer BCEs than those with non-AD triggers (19/98 [19%] vs 30/56 [54%]; OR: 0.21; 95% CI: 0.09-0.42; $P < 0.0001$) (Table 2, Figure 2). In the LQTS cohort, 9 of the 54 patients with AD triggers (17%) experienced >1 BCE after LCSD compared with 30 of the 51 with non-AD triggers (59%; OR: 0.14; 95% CI: 0.05-0.36; $P < 0.0001$) (Table 2, Figure 3A).

In a multivariable logistic model adjusting for baseline QTc (per 10-ms increase), AD (vs non-AD) triggers were associated with lower odds of post-LCSD events (adjusted OR: 0.20; 95% CI: 0.08-0.53; $P = 0.001$), and higher baseline QTc remained independently associated with events (adjusted OR: 1.17 per 10 ms; 95% CI: 1.06-1.30; $P = 0.003$).

Among CPVT patients, all post-LCSD BCEs occurred in those with AD triggers (10/44; 23%), with none recorded in the 5 patients with non-AD triggers. The small size of the non-AD group (n = 5) limited the statistical power to detect a significant difference ($P = 0.57$) (Table 2, Figure 3B).

BCEs AMONG LQTS GENOTYPES. The distribution of pre-LCSD triggers varied across different LQTS genotypes (Table 3). Among LQT1 patients, BCEs were significantly less frequent in those with AD-triggered CEs than in those with non-AD triggers (9/47 [19%] vs 8/16 [50%]; OR: 0.24; 95% CI: 0.08-0.72; $P = 0.02$) (Table 3). Although there were far fewer patients with pre-LCSD AD-triggered CEs among the other LQTS genotypes, no BCEs occurred in patients with AD-triggered CEs in LQT2 (0/6), LQT3 (0/1), or LQT Minor (0/3). However, small sample sizes limited

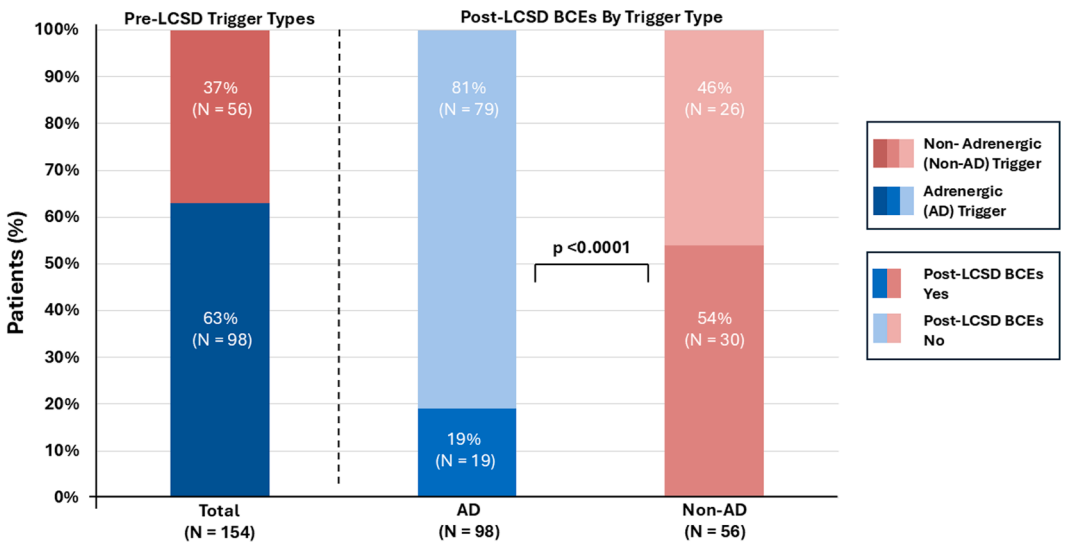
TABLE 3 Impact of LQTS Genotype and Pre-LCSD Trigger Type on Post-LCSD Cardiac Events

	Pre-LCSD Trigger Type	Post-LCSD BCE	No Post-LCSD BCE	OR (95% CI)	*P* Value
LQT1 (n = 63)	AD: 47 (74)	9 (19)	38 (81)	0.24 (0.08-0.72)	0.02[a]
	Non-AD: 16 (26)	8 (50)	8 (50)		
LQT2 (n = 26)	AD: 6 (23)	0 (0)	6 (100)	N/A	0.06
	Non-AD:: 20 (77)	9 (45)	11 (55)		
LQT3 (n = 10)	AD: 1 (10)	0 (0)	1 (100)	N/A	0.2
	Non-AD: 9 (90)	8 (88)	1 (12)		
LQT Minor (n = 10)	AD: 3 (30)	0 (0)	3 (100)	N/A	0.03[a]
	Non-AD: 7 (70)	6 (85)	1 (15)		

Percentages represent the proportion of patients with AD triggers relative to total patients in each cohort. ORs were calculated based on the formula (events A/nonevents A)/(events B/nonevents B). N/A indicates that because no events occurred in the AD group, an OR calculation was not performed. *P* values were derived by means of Fisher test.
[a]$P < 0.05$.

AD = adrenergic; BCE = breakthrough cardiac event; CPVT = catecholaminergic polymorphic ventricular tachycardia; LCSD = left cardiac sympathetic denervation; LQT1, 2, or 3 = long QT syndrome type 1, 2, or 3; LQTS = long QT syndrome; NA = not applicable.

FIGURE 2 Symptom Triggers and Outcomes in the Total Cohort



Bar chart showing the distribution of AD- and non-AD-triggered CEs and post-denervation BCEs by trigger type. The first bar represents the proportion of symptoms as AD-triggered (blue) and non-AD-triggered (red) CEs. The second and third bars show the incidence of BCEs by pre-procedure trigger type, whereby the darker colors represent the frequency of post-LCSD BCEs for AD (darker blue) and non-AD (darker red) pre-LCSD triggers. A BCE was defined as the recurrence of arrhythmia after the LCSD procedure. BCE = breakthrough cardiac event; other abbreviations as in Figure 1.

statistical comparisons with non-AD groups, in which BCEs were more common (LQT2: 9/20 [45%; $P = 0.06$]; LQT3: 8/9 [88%; $P = 0.20$]; LQT Minor: (6/7 [85%; $P = 0.03$]) (Table 3).

In the non-AD subgroup, paired Wilcoxon signed rank tests demonstrated a significant reduction in the number of events after LCSD in LQT1 ($P = 0.002$), LQT2 ($P = 0.002$), and CPVT ($P = 0.03$). No significant reduction was observed in LQT3 ($P = 0.3$) or LQT minor ($P = 0.6$). These findings confirm that, although LCSD exerts the strongest effect in patients with AD triggers, there is still measurable benefit in selected non-AD genotypes. To further illustrate this heterogeneity, we generated spaghetti plots stratified by genotype (LQT1, LQT2, LQT3, LQT Minor, CPVT), which depict individual trajectories of event burden before and after LCSD and show a decrease in CEs for the majority of patients (Supplemental Figure 1).

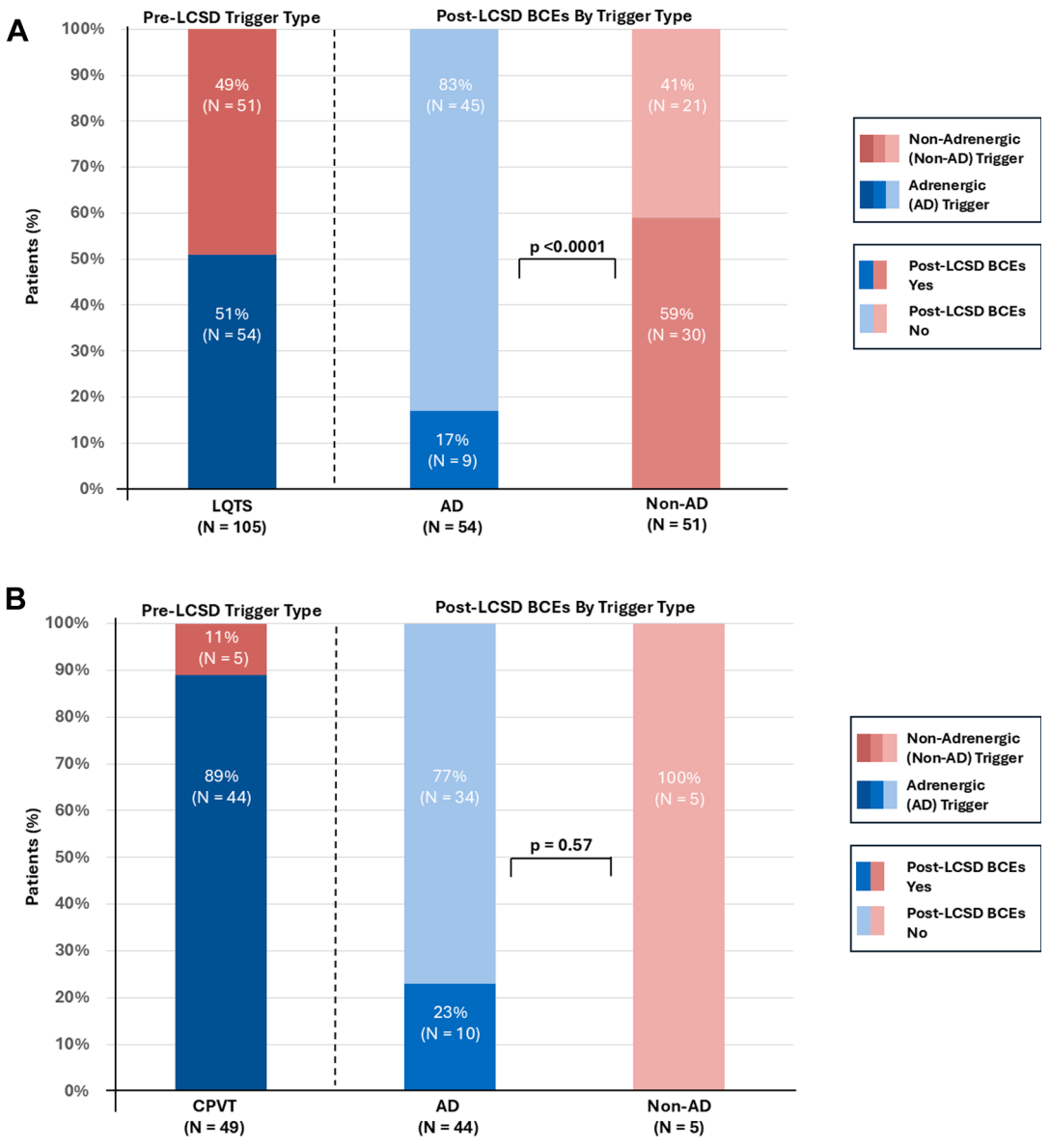
POST-LCSD PHARMACOLOGIC AND PROCEDURAL INTERVENTIONS. Among the 154 patients, 105 did not have any recurrence of CEs after LCSD. Of these 105 patients, 78 remained on the same therapy, although for 27 (25%) pharmacologic treatment was altered: 20 patients discontinued β-blockers because of intolerance (17 LQTS and 3 CPVT; 15 with AD and 5 with non-AD triggers), 6 CPVT patients had flecainide added because of increased PVC burden on follow-up stress testing, and 1 LQT2 patient had mexiletine added because of extreme QT prolongation (>540 ms).

In contrast, 49 of the 154 patients (31.8%) experienced >1 recurrence. Of these 49 patients, 22 (44%) required increase of their drug doses, and others underwent more extensive interventions, including right-side denervation (n = 6), repeated LCSD to ensure proper extent of ganglion removal (n = 1), heart transplantation (n = 3), or initiation or resumption of additional therapies such as mexiletine, flecainide, β-blockers, and atrial pacing, or multiple changes based on event burden.

DISCUSSION

LQTS and CPVT are inherited cardiac channelopathies predisposed to ventricular arrhythmias, often triggered by AD stimulation.[4,13] In LQTS, sympathetic activation, primarily through β-adrenergic pathways, exacerbates early after-depolarizations and increases transmural dispersion of repolarization, facilitating torsades des pointes.[14] These effects are particularly evident in LQT1 and LQT2, where AD triggers prolong the cardiac action potential.[13] Not surprisingly, beta-blockers have been the cornerstone of therapy for LQTS, because they blunt the effects of AD stimulation, decreasing the likelihood of arrhythmogenic events.[7]

FIGURE 3 Symptom Triggers and Outcomes in LQTS and CPVT Cohorts

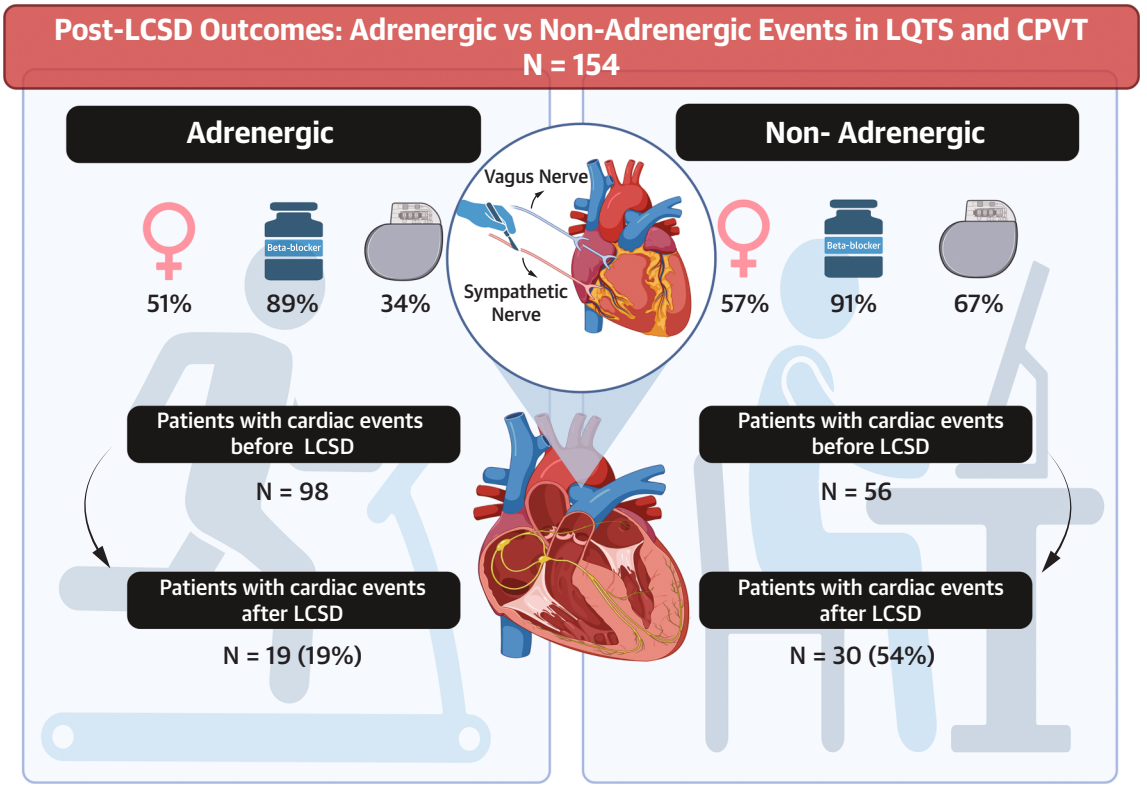


Bar charts illustrate the distribution of AD- and non-AD-triggered CEs and post-denervation BCEs by trigger type for the (A) LQTS and (B) CPVT cohorts. The first bar represents the proportion of symptoms as AD-triggered (blue) and non-AD-triggered (red) CEs. The second and third bars show the incidence of BCEs by pre-procedure trigger type, whereby the darker colors represent the frequency of post-LCSD BCEs for AD (darker blue) and non-AD (darker red) pre-LCSD triggers. A BCE was defined as the recurrence of arrhythmia after the LCSD procedure. Abbreviations as in Figures 1 and 2.

In CPVT, AD stimulation is a key arrhythmia trigger, where the mechanism is driven by defective calcium handling in cardiomyocytes.[15] Mutations in genes such as *RYR2* lead to aberrant calcium release from the sarcoplasmic reticulum during AD stimulation, causing delayed after-depolarizations and triggered activity.[4,15] As with LQTS, beta-blockers are the first-line treatment for CPVT, reducing AD drive and preventing calcium overload. Increasingly, combination drug therapy with the addition of flecainide is becoming the pharmacologic treatment of choice for CPVT.[16,17]

LCSD is an important and effective therapeutic modality in the management of refractory

CENTRAL ILLUSTRATION **Comparing AD and Non-AD Cohorts**



Vizentin VK, et al. JACC Clin Electrophysiol. 2026;■(■):■–■.

Key comparisons include the proportion of female patients, β-blocker use, and the presence of ICDs. In addition, the illustration highlights the distribution of BCEs in the total cohort after LCSD. AD = adrenergic; BCE = breakthrough cardiac event; CPVT = catecholaminergic polymorphic ventricular tachycardia; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome; non-AD = nonadrenergic.

arrhythmias in both LQTS and CPVT, mainly when pharmacologic therapy is insufficient or not tolerable.[12,18] By surgically reducing norepinephrine release to the myocardium of the left ventricle, LCSD reduces AD stimulation that drives the underlying mechanisms of arrhythmogenesis in these conditions. LCSD complements adjunctive therapies such as flecainide in CPVT by enhancing arrhythmia control and reducing implanted cardioverter-defibrillator shocks.[9] It has significantly improved arrhythmic outcomes, underscoring its value as a tailored approach for patients with refractory CEs.[12] The present study expands on these foundational principles, providing novel insights into the role of the underlying trigger, specifically AD vs non-AD triggers, in determining LCSD outcomes (**Central Illustration**).

In this study, we found that the type of pre-LCSD symptom trigger significantly influenced post-LCSD arrhythmic outcomes. Patients with AD-triggered CEs, particularly in LQTS, and most notably LQT1, showed a markedly lower incidence of post-LCSD BCEs than those with non-AD-triggered CEs. These findings are consistent with the AD mechanisms underlying arrhythmogenesis in these subtypes and support the targeted efficacy of LCSD in mitigating sympathetic-mediated risk. In CPVT, where arrhythmia is primarily AD driven, the low number of non-AD cases limited direct comparison; however, the overall low BCE rate observed after LCSD in our CPVT cohort reinforces the role of LCSD in controlling AD-dependent arrhythmias.

These findings align with previous studies emphasizing the clinical relevance of event triggers in LQTS management.[3,19] As previously shown by Younis et al,[11] syncope triggers had a key role in phenotype assessment and risk stratification in LQTS types 1 to 3. Kim et al[20] reported that beta-blockers are most effective for exercise-induced events, but less so for arousal- or non-AD-related episodes. Goldenberg et al[21] further noted that AD-triggered

events, especially those related to exercise or arousal, respond well to beta-blockers, whereas events during rest or sleep are less influenced by AD modulation.

Subtype analysis of LCSD outcomes in LQTS further reinforced the nuanced role of genotype in determining outcomes.[3,22] LQT1 patients were more likely to have AD-triggered symptoms, which is consistent with the known association between LQT1 events and exercise or sustained AD tone. Notably, no post-LCSD BCEs were observed in LQT2 patients with AD triggers, suggesting a potential protective effect of LCSD even in that subtype. Although the sample size was small, this finding aligns with previous studies indicating that LQT2 arrhythmias often follow sudden, transient surges in sympathetic activity, such as startle responses or arousal. LCSD may blunt these acute adrenergic spikes, stabilizing cardiac repolarization and reducing arrhythmia risk.

STUDY LIMITATIONS. This study has some limitations that warrant consideration. First, although the sample size is one of the largest cohorts of LCSD patients reported to date, the numbers of patients in some subgroups, especially CPVT with non-AD triggers and LQTS subtypes beyond LQT1, were small, limiting our ability to draw statistically robust conclusions in those subsets about differential therapeutic efficacy based on pre-LCSD trigger type. Second, classification of symptoms into AD and non-AD relied on retrospective clinical documentation and patient or family recall, which introduces variability, recall bias, and potential underreporting, particularly for non-life-threatening symptoms such as syncope, whose documentation may vary over time across the 20-year study period. Although secular trends in, for example, surgical methods, standards, or disease detectability could be expected to influence results over this time span, stratified analyses in blocks of time did not show any era effects on observed associations or outcomes (Supplemental Tables 3 and 4).

Although we attempted to refine classification by detailing specific contexts, unrecognized or undocumented triggers may have influenced some events, introducing possible misclassification bias. Events during early recovery were classified as AD, consistent with persistent sympathetic activation in this phase, but we recognize these ultimately may differ mechanistically from events during peak exertion. Similarly, events occurring during sleep that we classified as non-AD may still have been driven by unrecognized AD surges, such as auditory stimuli, oxygen desaturation, or transient blood pressure surges. These factors highlight that our AD vs non-AD terminology serves as a pragmatic clinical framework rather than a definitive pathophysiologic construct. And third, although follow-up was extensive, extending up to 2 decades for some patients, the potential remains for underreporting of BCEs.

CONCLUSIONS

With one of the largest LCSD cohorts to date, this study highlights the impact of pre-procedure CE trigger type on outcomes among previously symptomatic patients with either LQTS or CPVT. LCSD was particularly effective in reducing BCEs among those with AD-triggered CEs, especially in LQT1, supporting its role as a precision therapy in inherited arrhythmias. By integrating pathophysiologic insights with clinical outcomes, our findings reinforce the value of trigger-based individualized LCSD candidacy. Future studies should further explore LCSD effects in non-AD pathways and its potential synergy with emerging therapies.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: LCSD is an effective adjunctive therapy for reducing BCEs in patients with inherited arrhythmias, especially those with AD-triggered CEs, such as CPVT and LQTS. Careful phenotyping and evaluation of CE triggers can guide patient selection for optimal outcomes.

TRANSLATIONAL OUTLOOK: Assessing CE trigger type in channelopathy evaluations could refine risk stratification and guide the use of treatments such as LCSD. LCSD may offer improved outcomes for patients with persistent risk despite optimal medical therapy by tailoring interventions based on trigger-specific mechanisms.

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KEY WORDS adrenergic, catecholaminergic polymorphic ventricular tachycardia, left cardiac sympathetic denervation, long QT syndrome

APPENDIX For the supplemental figure and tables, please see the online version of this paper.