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Bilateral cardiac sympathetic denervation in children with long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia

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Introduction

Channelopathy, which may cause specific arrhythmias, such as long-QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) in children, leads to ventricular tachycardia and fibrillation, which are life-threatening in nature. An increase in sympathetic stimulation, which is responsible for triggering such arrhythmias, is often resistant to antiarrhythmic treatment. Modulation of the cardiac autonomic nervous system is now being used frequently in the treatment of channelopathy. Cardiac sympathetic denervation (CSD) is carried out via surgical excision or pharmacological inhibition of the extrinsic thoracic sympathetic chain (SC). For this reason, left CSD (LCSD) has been shown to decrease the number of sudden deaths and events in cases of CPVT and LQTS [1].

LCSD is frequently carried out in medical-resistant pediatric channelopathy; however, no bilateral CSD (BCSD) series for children has been presented in the literature. Some articles report low recurrence rates in adults who undergo BCSD compared to LCSD [2]. Therefore, the bilateral approach may also reduce recurrence rates of sympathetic denervation in pediatric patients. The aim of this study is to present the initial results for pediatric cases where BCSD was carried out to treat LQTS and CPVT.

Methods

Patients and methods

In this retrospective study, data from 156 patients with ventricular arrhythmia at our tertiary hospital's pediatric cardiology arrhythmia clinic were collected between September 2011 and April 2019. 135 patients had LQTS and 21 had CPVT. Implantable cardioverter-defibrillators (ICDs) were implanted in 26 LQTS patients and 17 CPVT patients according to the HRS/EHRA/APHRS expert consensus [3]. The research team agreed that LCSD would be indicated in patients who had an intolerance for medical treatment, who continued to experience ICD shocks despite optimal care, who refused to be implanted with an ICD, and in those with CPVT in whom a primary prevention operation was indicated due to a family history of cardiac arrest. LCSD is accepted as the standard surgical procedure for denervation in patients with CPVT and LQTS [1]; thus, we performed LCSD in the first two patients who were referred from the arrhythmia clinic. One patient with CPVT and one with LQTS underwent LCSD; however, both patients were admitted to the pediatric clinic after six months due to recurrent events. After this clinical experience, we decided to perform BCSD initially in patients with channelopathy. Patients who underwent LCSD followed by right CSD (RCSD) due to recurrence were excluded from the research. This study was granted approval by our hospital's Ethical Committee (2018/63). Informed consent was obtained from patients' families as needed.

15 patients were included in our study for a video-assisted thoracoscopic surgery (VATS) BCSD operation. Four patients had a history of epilepsy and seven had a family history of sudden death. In total, eight of the 26 LQTS patients and six of the 17 CPVT patients who had frequent shocks were included. Additionally, one patient with CPVT who did not have an ICD underwent BCSD for primary prevention. The reasons for inclusion are summarized in Table 1. Patients' demographic characteristics, operational data, medical treatment, ICD records, and monitoring data were assessed in detail.

Surgical technique

All operations were performed by a single surgical team. In the supine position, both arms were opened at an angle of 90°. All patients were intubated with a single-lumen endotracheal tube, and an external defibrillator pad was attached to the posterior and anterior regions of the thorax. Their ICD devices were then switched off. After all required coverings were carried out, the head of the operating table was tilted up by 45° and rotated 30° away from the side on which the operation was due to be performed. Operations were carried out on patients' left sides first. The fourth intercostal space (ICS) was opened into the first port middle axillary line, and CO_2 insufflation commenced. A camera was used to visualize the scene, while the second port was placed into an anterior axillary line through the third ICS. A minimally invasive two-port VATS procedure was performed. Then, CO_2 insufflation was adjusted to a pressure of 6 mmHg. In several patients, it was impossible to achieve sufficient exposure at this pressure, so insufflation was increased up to 8–10 mmHg. When this failed to result in sufficient exposure, the third

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Table 1
Patient characteristics.

No.	Age	Sex	Arrhythmia	Antiarrhythmic	Dose/daily	Period between ICD-BCSD (months)	Mutation	Family history of sudden death
1	4	F	LQTS-JLNS	NAD	1	5	KCNQ1	
2	17	F	CPVT	PRP + FLC	3 + 100	1	–	2 siblings
3	12	M	CPVT	PRP + FLC	3 + 100	3	CASQ2	
4	14	M	CPVT	PRP + FLC	3 + 100	64	–	Father
5	15	F	LQTS-7	PRP	3	–	KCNJ2	2 siblings
6	14	F	LQTS-7	PRP	3	10	KCNJ2	
7	9	M	LQTS-JLNS	PRP	3	72	KCNQ1	Cousin
8	13	M	CPVT	PRP	3	50	RYR2	
9	15	F	CPVT	PRP + FLC	3 + 100	48	–	
10	17	M	CPVT	PRP	3	72	–	
11	7	M	LQTS-1 + 2	PRP	3	41	KCNQ1+ KCNH2	1 sibling, mother
12	14	M	LQTS-1	PRP	3	54	KCNQ1	1 sibling
13	10	F	LQTS-7	PRP + FLC	3 + 100	50	–	
14	7	M	LQTS-JLNS	PRP	3	8	KCNQ1	
15	15	M	CPVT	PRP + FLC	3 + 100	60	–	Father, 2 cousins

F: female M: male LQTS: long-OT syndrome, CPVT: catecholaminergic polymorphic ventricular tachycardia JLNS: Jervell and Lange Nielsen syndrome, LQTS-7: Andersen Tawil syndrome, NAD: nadolol, PRP: propranolol, FLC: flecainide, dose/daily: mg/kg/day for NAD and PRP, mg/m^2/day for FLC.

port was placed at the fifth ICS through the anterior axillary line to retract the lung. Electrocautery was used to separate T2–4 ganglions, beginning from the SC T1 distal rami communicans (Kuntz nerves) and spinal nerves (Fig. 1). Kuntz nerves were cauterized to 1 cm from the medial and at least 2 cm from the lateral. Subsequently, T2, T3, and T4 ganglions were totally cauterized to execute sympathetic denervation. The location of the port was sutured once CO_2 was totally discharged from the thorax cavity. Rarely, the discharge of air persisted in some patients, so a thoracic drain was inserted. The thoracic drain tube was connected to an underwater drainage system. The same surgical procedures were repeated after passing to the contralateral side. The ICD device was restarted after the operation during a weaning period, and patients were taken to the intensive care unit. Patients were continuously monitored for 24 h.

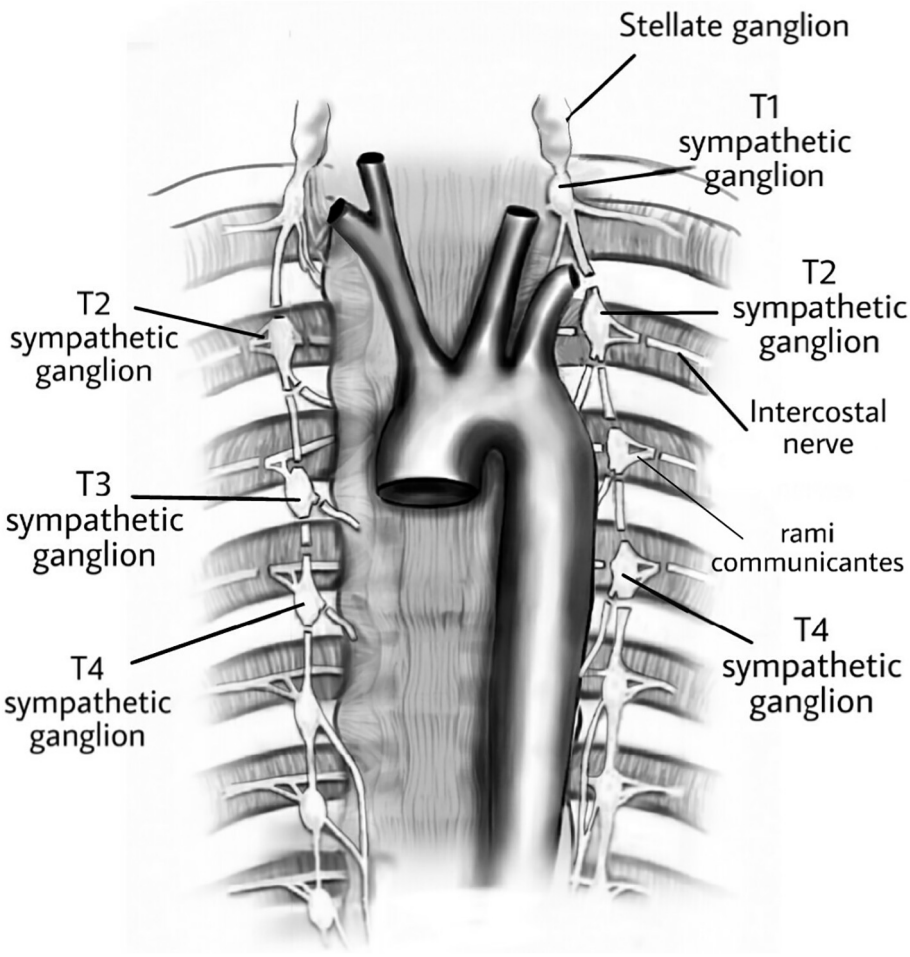

Fig. 1. Illustration of bilateral cardiac sympathetic denervation.

Statistical analyses

Data was analyzed using SPSS software version 20.0 (IBM Inc., Chicago, IL, USA). Variable distribution normality was assessed using the Shapiro-Wilk test. Continuous abnormal variables were shown as median (min–max) values. Categorical variables were shown as numbers and percentages. A Wilcoxon signed-rank test was used to compare dependent continuous variables. Statistical significance was set at $p < 0.05$.

Results

In total, BCSD operations were conducted on 15 patients. Of these, nine patients (60%) were male, and six (40%) were female. Patients' median age was 14 years (4–17). The patients' data are shown in Table 2. A video-thoracoscopic BCSD operation using two ports was conducted on 11 patients, and the same operation using three ports was conducted on four patients. The median operation duration was 43 min (22–65). In all patients, sympathetic denervation was achieved through the electrocautery of sympathetic ganglions and Kuntz fibers. All patients remained on the same medications/doses following the surgery.

Complications were as follows: one LQTS patient experienced perioperative polymorphic ventricular tachycardia, which went into the sinus through perioperative electroshock, and one CPVT patient had a prolonged air-leak. In addition, alternate sweating was spotted in one CPVT patient and one LQTS patient in the follow-up. A unilateral thoracic drain was inserted into four patients during their operations due to the preoperative continuous air leak. The thoracic drains of three patients were removed on the first post-operative day, while a postoperative air leak lasted two days in one patient. Most importantly, no cases showed any sign of Horner syndrome, and there was no mortality.

The median duration of hospitalization was one day (1–3). The median monitoring period after BCSD was 22 months (12–73). The number of preoperative shocks in those with ICDs after BCSD fell from 13 (0 −30) to 0 (0–3) in one year in the postoperative period ($Z = -3.29$, $p = 0.001$). A total resolution of shocks (100%) was detected in 60% of patients ($n = 9$) after BCSD (two out of seven CPVT patients and seven out of eight LQTS patients). One LQTS patient who had BCSD as a primary prevention was followed clinically because there was no ICD. A satisfactory partial resolution (88%) was detected in 40% of patients ($n = 6$) without recurrence (five out of seven CPVT patients and one out of eight LQTS patients) (Table 2). In addition, cohort's both pre-operative and post-operative heart rates, PR, QRS, QT levels and corrected QT (QTc) interval on electrocardiogram (ECG) by using Bazett, Frederichia, Framingham and Hodges formulas are given in Table 3. There is no significant difference between pre-operative and post-operative PR, QRS, QT and QTc values; but, there is significant difference in pre-operative and post-operative heart rates ($p = 0.003$).

Discussion

The sympathetic nervous system plays a significant role in the progress of ventricular arrhythmias. Certain arrhythmias, such as CPVT and LQTS, have characteristics that affect a person's survival. The progress of these diseases is caused by sympathetic stimulation in vulnerable individuals who do not respond to anti-arrhythmic agents. It has been stated that 46–69% of patients with channelopathy continue to have cardiac events despite maximum therapy [4]. In such cases, ICDs may be used to prevent sudden deaths. Ironically, ICD shocks may trigger arrhythmias depending on the sympathetic stimulation, as they can cause "electrical storms." Furthermore, ICD is not ideal in pediatric patients due to extreme sensitivity to catecholamines released as a consequence of anxiety and pain associated with ICD shocks.

Up until now, LCSD has commonly been carried out because patients experienced multiple appropriate shocks due to ICD. In the Heart Rhythm Society's guidelines on primary inherited arrhythmia syndromes, Class I LCSD is recommended for patients with LQTS who are resistant to or unable to use beta blockers, those who refuse an ICD device, or those who have symptoms despite the implantation of an ICD. Similarly, Class IIb LCSD is recommended during the use of beta blockers in CPVT cases, in cases in which beta blockers are contraindicated, or in cases in which syncope or ICD-originated shock has been observed [3]. In addition, there are several case reports that present renal sympathetic denervation is also beneficial in pediatric [5] and adult patients [6] with catecholaminergic polymorphic ventricular tachycardia.

In patients with severe ventricular arrhythmias, LCSD lessens the frequency of ventricular arrhythmias and sudden death of cardiac origin [7,8]. Research has shown that LCSD has been an effective treatment for many types of CPVT and LQTS [9,10]. Atallah et al. [11] reported the full recovery of three in four children with CPVT (75%) after LCSD, whom they monitored themselves. In addition, LCSD has been shown to be effective in cases of CPVT and LQTS in many studies at a rate of over 70% [12,13], though a recurrence rate of 24–66% has also been reported in several articles [12–15]. Nevertheless, LCSD for arrhythmias originating from a region controlled by the right-sided sympathetic nerves is likely to be ineffective. In cases where LCSD fails to hamper ventricular arrhythmias, an auxiliary treatment, RCSD, might be an alternative.

Table 2
Patients reasons and bilateral cardiac sympathetic denervation results.

No.	Diagnosis	Reason for BCSD	Preop-ICD shocks/year	Postop ICD shocks/year	Hospitalization (Days)	Complications	Follow-up (Months)
1	LQTS-JLNS	M-ICD shocks	13	3	2	Perop PVT	73
2	CPVT	M-ICD shocks	21	2	1	AS	60
3	CPVT	M-ICD shocks	13	2	3	0	32
4	CPVT	M-ICD shocks	22	3	2	0	24
5	LQTS-7	Primary prev.	No-ICD	No-ICD	1	0	23
6	LQTS-7	M-ICD shocks	25	0	1	0	22
7	LQTS-JLNS	M-ICD shocks	9	0	2	0	22
8	CPVT	M-ICD shocks	8	1	2	0	22
9	CPVT	M-ICD shocks	24	1	2	0	21
10	CPVT	M-ICD shocks	4	0	1	0	17
11	LQTS-1 + 2	M-ICD shocks + medication errors	20	0	1	0	15
12	LQTS-1	M-ICD shocks	1	0	1	AS	14
13	LQTS-7	M-ICD shocks + medication errors	30	0	1	0	13
14	LQTS-JLNS	M-ICD shocks	8	0	1	0	13
15	CPVT	M-ICD shocks	6	0	1	PAL	12

M-ICD shocks: multiple implantable cardioverter-defibrillators shocks, LQTS: long-OT syndrome, CPVT: catecholaminergic polymorphic ventricular tachycardia, JLNS: Jervell and Lange Nielsen syndrome, LQTS-7: Andersen Tawil syndrome, LCSD; left cardiac sympathetic denervation, Primary prev: primary prevention, Preop: preoperative, Postop: postoperative, Perop PVT: peroperative polymorphic ventricular tachycardia, AS: alternate sweating, PAL: prolonged air-leak.

Table 3
Patients' pre-operative and post-operative PR, QRS, QT levels and QTc interval on ECG by using Bazett, Frederichia, Framingham and Hodges formulas.

No.	Diagnosis	PR interval, (ms)/p = 0.934 [m]		QRS duration, (ms)/p = 0.588 [m]		QT interval, (ms)/p = 0.533 [m]		QTc Bazett, (ms)/p = 0.130 [m]		QTc Friderichia, (ms)/p = 0.319 [m]		QTc Framingham, (ms)/p = 0.262 [m]		QTc Hodges, (ms)/p = 0.221 [m]		HR/bpm/p = 0.003 [m]	
		Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
1	LQTS-JLNS	144	144	74	72	500	478	642	552	598	526	561	517	568	513	101	81
2	CPVT	148	154	92	96	408	416	453	453	438	440	437	440	443	435	74	67
3	CPVT	160	152	86	102	498	396	426	409	449	405	442	406	470	403	68	64
4	CPVT	152	158	88	92	389	402	441	422	423	416	423	415	419	413	77	66
5	LQTS-7	142	140	92	90	402	400	428	429	419	420	420	419	416	416	78	69
6	LQTS-7	170	168	78	72	446	422	449	439	441	440	443	440	443	436	68	58
7	LQTS-JLNS	132	138	86	89	445	430	520	485	494	462	486	465	484	458	82	76
8	CPVT	166	154	92	102	388	378	434	425	418	410	418	409	414	406	95	75
9	CPVT	156	163	98	90	379	403	454	448	427	432	427	432	425	428	86	74
10	CPVT	148	152	96	92	366	389	436	417	411	409	411	408	410	405	85	68
11	LQTS-1 + 2	171	178	86	84	422	403	429	426	427	419	427	418	426	415	72	67
12	LQTS-1	163	162	81	83	455	446	498	478	484	465	481	466	476	462	80	69
13	LQTS-7	167	169	79	85	420	404	443	434	429	430	430	429	427	425	72	64
14	LQTS-JLNS	129	139	99	95	465	466	512	489	492	480	487	481	483	477	73	66
15	CPVT	163	149	83	88	422	418	443	421	436	421	436	420	432	420	66	61

QTc: corrected QT interval, ECG: electrocardiogram, LQTS: long-QT syndrome, CPVT: catecholaminergic polymorphic ventricular tachycardia, JLNS: Jervell and Lange Nielsen syndrome, LQTS-7: Andersen Tawil syndrome, Pre-op: pre-operative, Post-op: post-operative, HR: heart rate, ms: milliseconds, bpm: beats per minute, m: Mann-Whitney *U* test.

Research has shown that RCSD lessens cardiac arrhythmia [16,17]. Lin et al. [18] reported that three of the six patients had undergone previous LCSD but developed arrhythmia recurrence; RCSD after prior LCSD was effective in suppressing these arrhythmias.

The thoracic sympathetic truncus has complex alternative ways of being carried out via the rami communicans [19]. Cadaver studies have shown that rami communicans are concentrated in bilateral T2 sympathetic ganglions, although fewer have also been observed in T3 and T4 ganglions [20]. In addition, it is stated that there is a functional asymmetry in the innervation of the heart. The left sympathetic nerve chain influences the left and posterior walls of heart innervation, and the right sympathetic nerve chain effects heart rate due to its stimulation on the sinus node [21].

There is a theoretical concern that even if LCSD is initially effective, the right cardiac sympathetic nerves may hypertrophy and extend nerve sprouts to regions subtended by the resected left-sided ganglia [22,23]. This process of remodeling in the right sympathetic nerves may induce the recurrence of arrhythmias. Kirgis et al. [24] reported that the incidence rate of two-sided and one-sided intercostal rami originating from the T2 nerve and connected to the T1 nerve was 59% and 31.8%, respectively, and the incidence rate of those originating from the T3 nerve and connected to the T2 nerve was 34.1% and 40.9%.

Vaseghi and Aijola presented that in adults, BCSD is more effective than LCSD [25,26]. In children, the safety and feasibility of BCSD for the control of ventricular arrhythmias has yet to be clarified [25]. A pediatric case report has suggested that BCSD is more effective than a unilateral operation [27]. In our study, recurrence emerged six months in the first two patients who underwent LCSD; therefore, RCSD was added. Given the multiple appropriate shocks, family concerns, and patient anxiety, the pediatric cardiology and surgical team decided to proceed with BCSD in a single session rather than proceed in a stepwise modality in pediatric patients. After performing BCSD, no recurrence was observed over the course of follow-up. We monitored a rate of full resolution in 60% of cases and a partial (88%) resolution in the remaining 40% of cases. It was thought that BCSD was more effective than LCSD.

Schwartz suggested that RCSD is appropriate in cases in which LCSD is inadequate; however, he did not recommend BCSD as the first-line approach, as it deprives the dysfunctional heart of the potentially beneficial adrenergic discharge of the cardiac sympathetic nerves on the right, affecting both ventricular ability to control heart rate [28]. While this may be true for adults and patients with disordered ventricular functions, such as cardiomyopathy, BCSD may not cause complications in pediatric cases of ventricular arrhythmias dependent on channelopathy without disordered ventricular functions.

Complications of LCSD are as follows: unilateral hand dryness, color or temperature variations between the sides of the face, and alterations in sweating patterns [22,25]. Another advantage of BCSD is that it does not create asymmetric discomfort, which may be caused by LCSD. For example, Antiel et al. conducted LCSD on 20 patients with LQTS and six patients with CPVT, showing that the most prevalent side effects in pediatric patients were unilateral hand dryness (84%), color or temperature differences between the sides of the face (76%), and inordinate sweating (54%) [29]. In our study, alteration in the sweating pattern was spotted in two patients (13.3%); one of them returned to normal after six months. In the literature, the rate of chronic Horner syndrome is 5%, while the rate of temporary signs of Horner syndrome varies from 23% to 48% [9,17,29,30]. It has been suggested that in order to prevent recurrence, the lower half of the stellate ganglion or the lower third of the stellate ganglion and the T1–T4 ganglions must be denervated [31]. In pediatric patients, Horner syndrome or its signs can be difficult for families to accept and may have psychosocial consequences. In our study, neither chronic nor temporary Horner syndrome, nor any of its signs, were observed in any case. A potentially lower risk of Horner syndrome in our study is not “an advantage” of the BCSD surgical technique; rather, it is the result of sparing the stellate ganglion. Our pediatric patients were not put at risk of Horner syndrome or its signs.

Limitations

This retrospective study was based on observation; therefore, patients were not randomly selected. The retrospective nature of this study prevented the inclusion of other factors in evaluating the outcomes of BCSD, such as comorbidities and previous ventricular arrhythmia storms. Hence, the effects of LCSD in this population may have been over- or under-estimated. If there was a control group of patients who underwent LCSD, comparing results with BCSD would have provided better insight into the topic.

Conclusion

Overall, BCSD seems to be an effective and reliable method of decreasing arrhythmic burden and the number of shocks in pediatric patients with LQTS and CPVT. The use of this method in the early stages of the disease may prevent recurrent ventricular arrhythmia storms and the incapacitating psychosocial effects attributed to ICD shocks.

Future prospective and randomized studies with larger cohorts are warranted to confirm the efficacy of BCSD as optimal treatment in the management of pediatric patients with LQTS and CPVT.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

The study was granted approval by the Ethical Committee (2018/63) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was retrospective designed.

Informed consent

Not obtained due to retrospective study design.

CRediT authorship contribution statement

Murat Akkuş: Conceptualization, Methodology, Formal analysis, Writing - original draft, Investigation, Project administration, Supervision. **Yunus Seyrek:** Formal analysis, Methodology, Writing - review & editing. **Hasan Candaş Kafalı:** Data curation, Investigation. **Yakup Ergül:** Data curation, Investigation, Supervision.

Declaration of competing interest

All of the authors have no conflicts of interest to report.

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