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Left cardiac sympathetic denervation in the management of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: A meta-regression

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Abstract

Background: Left cardiac sympathetic denervation (LCSD) has been proposed as useful therapy for long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), in addition to anti-arrhythmic agents and implantable cardioverter defibrillators. This study aimed to assess the current evidence for LCSD and compare the open vs the video-assisted thoracoscopic surgery (VATS) approaches.

Methods: MEDLINE, Embase and Cochrane library databases were searched up to December 2018 for studies reporting the long-term outcomes of LCSD in LQTS, CPVT patients. The incidence of cardiac events (CEs) before and after surgery, the change in QTc interval, and surgical complications were pooled to estimate the efficacy of LCSD. Meta-regression was used to estimate the effects of surgical approach (open vs VATS) on outcomes following LCSD.

Results: Twenty-seven papers met our inclusion criteria (647 patients). VATS was used in 408 patients (63.1%), open surgery in 239 (36.9%). Mean follow-up was 32.3 ± 32.5 months. Postsurgery, 398/585 patients (68.0%) were free of CEs and QTc decreased from 522 ± 61.6 ms to 494 ± 52.3 ms. Meta-regression showed no differences between the two approaches in the incidence of CEs and surgical complications. VATS was associated with a smaller reduction in QTc (β-coefficient −20.04, 95% CI −36.82 to −3.27, P = .019).

Conclusions: LCSD was associated with a reduction in the incidence of CEs in LQTS, CPVT patients and in the duration of QTc. Open surgery was associated with a greater reduction in QTc. Due to the limitations that hindered our study, a randomized trial is warranted to fully establish LCSD safety and efficacy.

KEYWORDS

CPVT, long QT syndrome, sudden cardiac death, sympathectomy, VATS

1 | INTRODUCTION

Long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are two major cardiac channelopathies. LQTS affects 1/2500 people and is caused by mutations in genes encoding ion channels involved in the control of ventricular repolarization.[1] CPVT affects 1/ 10,000 people, with mutations in the sarcoplasmic calcium channel ryanodine receptor 2 gene typically responsible for the condition.[2]

LQTS is characterized by prolonged ventricular repolarization, thus increasing the QT interval and predisposing patients to *torsades de pointes* and sudden cardiac death (SCD), whereas CPVT is characterized by ventricular tachycardia precipitated by exercise or emotional stress. Both entities are triggered under conditions of increased sympathetic activity.[3,4] Clinically, they present as episodic syncope, usually during physical activity or an emotional situation and at a young age. SCD is the most extreme presentation and can occur in previously asymptomatic patients.[4]

The management of LQTS and CPVT is difficult. β-blockers provide an effective first line treatment option.[5] However, up to 25% of patients are refractory to high-dose β-blocker therapy and side effects or intolerance to β-blockers may also limit their use, particularly in the severely asthmatic and elderly.[6] In such cases, other antiarrhythmic drugs have been suggested and the most recent guidelines for inherited primary arrhythmia syndromes recommend flecainide as a class IIb treatment for patients with LQTS and as a class IIa for CPVT patients.[5] When optimal medical treatment does not control symptoms, the insertion of an implantable cardioverter defibrillator (ICD) is performed.[7] However, this device presents important comorbidities, such as infections, psychological stress, malfunctions, inappropriate discharges, and the risk of electrical storm by repeated discharges.[7]

Faced with conditions refractory to medical therapy, left cardiac sympathetic denervation (LCSD) may have a role in directly reducing adrenergic stimulation.[8-10] The rationale for this intervention lies in the arrhythmogenic potential of the left stellate ganglion[11] and the demonstration of the antifibrillatory effect of left stellectomy.[12] Currently, with the rise of video-assisted thoracoscopic surgery (VATS), new approaches have emerged. This meta-analysis aims to evaluate the VATS approach vs open surgery for LCSD in LQTS and CPVT patients and to assess the evidence underpinning this.

2 | METHODS

2.1 | Search strategy

The review protocol was registered in PROSPERO (CRD42017064621). The review adhered to PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.[13] MEDLINE/PubMed, Embase and Cochrane Library were searched, without language restriction, from inception to December 19, 2018. Grey literature such as conference proceedings were excluded due to the high risk of incomplete data. Key words and MeSH terms pertinent to the exposure of interest were used in the following combination: (LQTS or LQTS or CPVT or Polymorphic catecholergic ventricular tachycardia) AND (LCSD or cardiac denervation or sympathectomy). References of all eligible studies were also screened to identify relevant resources that were not previously identified. As this study used publicly available data, no informed consent was required.

2.2 | Selection criteria

Two authors (AS, PLA) identified studies eligible for further review by performing an initial screen of titles/abstracts. Articles were considered for inclusion if they reported original data on the clinical outcomes after LCSD in patients with LQTS or CPVT. All LQTS genotypes were included. The following study designs were included: prospective cohort, retrospective cohort, case series, controlled and randomized clinical trial. Reviews, editorials, and case reports were excluded. A second screening based on detailed full-text review was performed. Any disagreement was resolved by consensus. The exposure of interest was open or VATS approach. The primary outcomes of interest were the postoperative percentage of patients with major cardiac events (CEs) despite optimal medical therapy and the rate of recurrence of major CEs after surgery.

2.3 | Data extraction and quality assessment

Year of publication, study design, country, sample size, recruitment period, baseline patient demographics, surgical approach, and outcomes among relevant subgroups of patients were extracted. The NIH Quality Assessment Tool for Case Series Studies was used to assess study quality.[14]

2.4 | Outcomes

The outcomes of interest were defined as follows. Patients were considered responsive to treatment if they experienced less CEs in the postoperative period compared to before surgery. For this analysis, a CE was defined as either ICD shock, syncope, aborted cardiac arrest (ACA), or SCD. Patients were considered symptomatic for their underlying arrhythmic disease if they had at least one syncope or ACA or SCD during the follow-up. Patients not experiencing any CEs after surgery were defined free of CEs. The surgery side effects of interest were the clinical diagnosis, either temporary or definitive, of Horner's syndrome and asymmetric facial sweating.

2.5 | Statistical analysis

The event rates were extracted from primary studies for binary outcomes, and means and standard deviations for continuous outcomes. Operative approach (VATS or open surgery) was taken as the explanatory variable. When the included studies reported the median, range and sample size, the mean and standard deviation were estimated using Luo et al and Wan et al methods, respectively.[15,16] To obtain a numerical estimate which would be of use for future

trials and research in the field, in addition to quantifying the heterogeneity contained within study populations, we planned to conduct a meta-analysis of incidence rates and average change. To avoid bias from low event rates and sample sizes, studies included in the meta-analysis had to include ≥10 patients. For binary outcomes, incidence rates of the outcome of interest were divided by length of follow-up (measured in person years) to give summarized incidence rates per person years. Incidence rate meta-regression was performed, using a residual maximum likelihood model (random effects), with operative approach set as the explanatory variable of interest. The effect estimate is presented as change in incidence rate per person years. Estimates are expressed in terms of average incidence rate change for each operative approach. For continuous variables, the weighted mean difference was estimated using a residual maximum likelihood model. For all meta-regression, the effect of the open approach was also the model intercept. Statistical heterogeneity was evaluated using the I^2, with <25% indicating low heterogeneity, 50%-75% moderate heterogeneity, and >75% high heterogeneity. Substantial statistical heterogeneity between studies was defined as when I^2 > 50%. Meta-regression analysis of outcomes based on type of surgical approach (open vs VATS) was performed. All analyses were performed using R version 3.2.2 (R Foundation for statistical computing, Vienna, AUT) with the metafor package version 1.9-8. *P* values <.05 were considered statistically significant *a priori*.

3 | RESULTS

3.1 | Study selection and characteristics

We identified 557 potentially relevant studies (Figure 1). By reviewing title/abstract, 519 articles were excluded. The full text of the remaining articles was reviewed and 11 of these were subsequently excluded. Twenty-seven studies with 647 patients were included in our study. The characteristics and surgical outcomes of the included studies are listed in Tables 1 and 2, respectively.

Thirteen enrolled both LQTS and CPVT patients,[17,18,20-22,26-28,34,35,38,40,42] 11 only LQTS[19,24,25,29-32,36,37,39,41] and three only CPVT.[23,33,43] In 16 studies, VATS was the preferred approach[17-20,22,24,26-28,30-32,34,40-42] while in 8 studies open surgery was performed.[25,30,33,36-39,43] In three studies, patients were operated either with a thoracoscopic or an open approach, but only in one of them data were presented divided in VATS and open subgroups.[21] Therefore, the data of the remaining two studies (De Ferrari et al, no. of patients = 63; Olde Nordkamp et al, no. of patients = 16) were not included in the meta-analysis.[23,35] Twenty-four studies were rated Good according to the NIH Quality Assessment Tool for Case Series Studies and three were rated Fair (Table 1).

We identified 512/647 (79.1%) patients with LQTS and 135 (20.9%) with CPVT. Most patients were on β-blockers at the

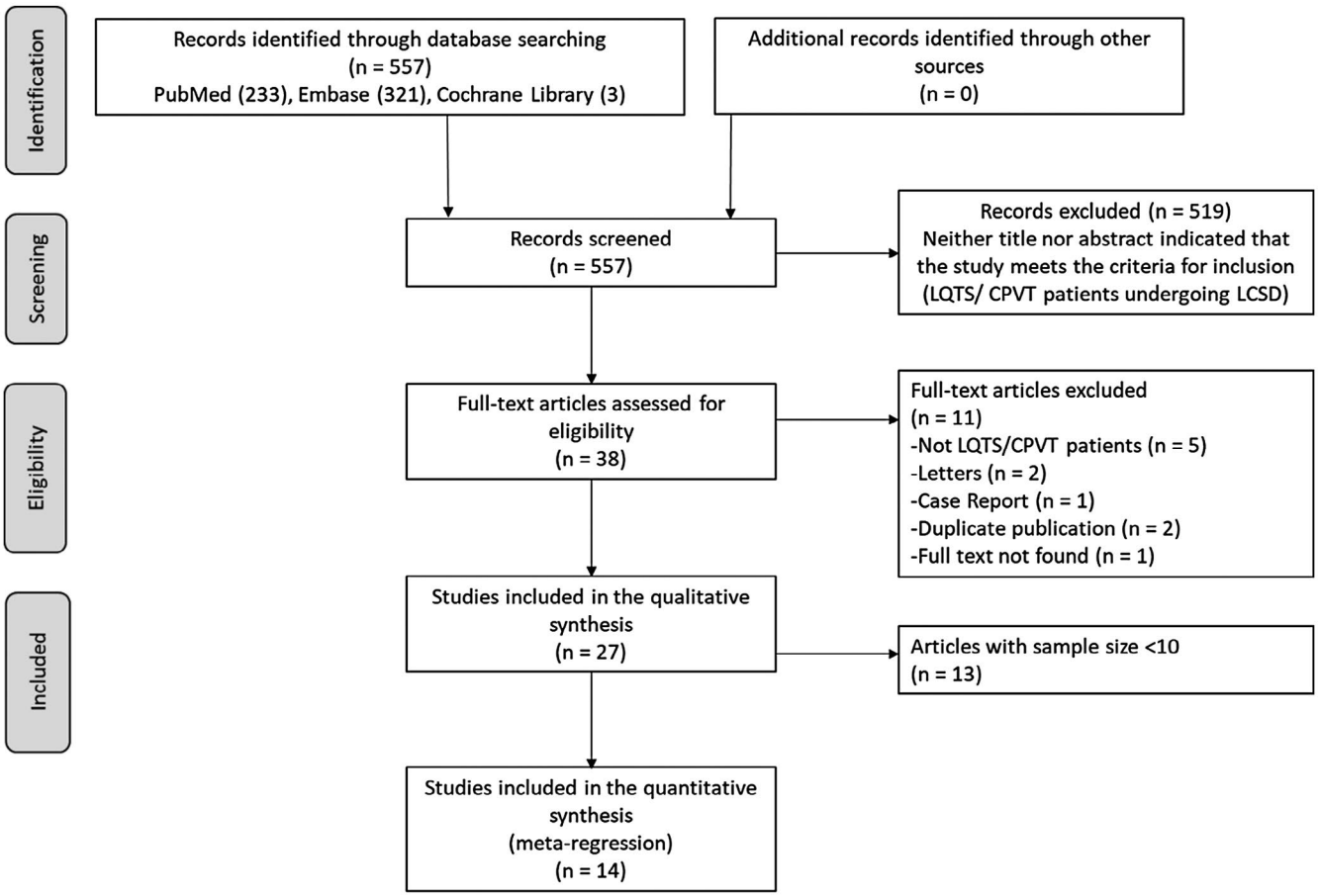

FIGURE 1 PRISMA flow diagram showing identification and exclusion process for review

TABLE 1 Baseline characteristics of included studies

First author	Year	Country	Study period	Study type	Sample size	Female (%)	Age, y (mean ± SD)	Population: A = adults, C = children, I = infants	Time of follow-up, mo (mean ± SD)	Inherited arrhythmic disease	QTc, ms (mean ± SD)	Symptomatic before surgery, n (%)	Therapy before surgery	Indication for treatment	Quality assessment
Antiel et al[17]	2016	USA	Nov 2005-May 2013	CS	62	38 (61%)	21.0 ± 16.6	A = 36, C = 26	37.2 ± 40.8	LQTS, CPVT	NA	NA	β-blockers NA, ICD 29/61 (48%)	PP 14/62 (23%), SP 48/62 (77%)	Good
Atallah et al[18]	2008	USA	2000-2008	CS	9	5 (56%)	8.6 ± 6.9	A = 1, C = 8	18.8 ± 19.9	LQTS, CPVT	463 ± 72	8/9 (89%)	β-blockers 9/9 (100%), ICD 5/9 (56%)	PP 1/9 (11%), SP 8/9 (89%)	Good
Bos et al[19]	2013	USA	Nov 2005-Dec 2010	CS	52	28 (54%)	14.1 ± 10.0	A, C	43.2 ± 15.6	LQTS	528 ± 74	34/52 (65%)	β-blockers 51/52 (98%), ICD 16/52 (31%)	PP 33/52 (63%), SP 19/52 (37%)	Good
Coleman et al[20]	2012	USA	Nov 2005-Dec 2011	CS	18	9 (50%)	14.0 ± 7.2	A = 4, C = 14	19.2 ± 18.0	LQTS, CPVT	NA	13/18 (72%)	β-blockers 16/18 (89%), ICD 6/18 (33%)	PP 5/18 (28%), SP 13/18 (72%)	Good
Collura et al[21]	2009	USA	Nov 2005-Nov 2008	CS	20	8 (40%)	9.1 ± 9.7	A = 1, C = 16, I = 3	16.6 ± 9.5	LQTS, CPVT	518 ± 70	16/20 (55%)	β-blockers 11/20 (55%), ICD 8/20 (40%)	PP 9/20 (45%), SP 11/20 (55%)	Good
Costello et al[22]	2015	USA	May 2011-Apr 2014	CS	10	NA	11.1 ± 6.0	C = 10	14.3 ± 11.3	LQTS, CPVT	482 ± 48	8/10 (80%)	β-blockers 10/10 (100%), ICD 5/10 (50%)	PP 0/10 (0%), SP 10/10 (100%)	Good
De Ferrari et al[23]	2015	Worldwide	1988-2014	CS	63	31 (51%)	14.3 ± 4.5	NA	43.6 ± 28.2	CPVT	NA	54/63 (86%)	β-blockers 61/63 (97%), ICD 32/63 (51%)	PP 9/63 (14%), SP 57/63 (86%)	Good
Desimone et al[24]	2015	USA	Nov 2005-May 2012	CS	72	40 (54%)	14.0 ± 10.0	NA	26.4 ± 20.4	LQTS	505 ± 56	38/72 (53%)	β-blockers 67/72 (93%), ICD 18/72 (28%)	PP 34/72 (47%), SP 38/72 (53%)	Good
Epstein et al[25]	1996	USA	NA	CS	5	5 (100%)	28.0 ± 3.0	A = 5	18.0 ± 12.0	LQTS	640 ± 54	5/5 (100%)	β-blockers 4/5 (80%), Pacemaker 3/5 (60%)	PP 0/5 (0%), SP 5/5 (100%)	Good
Garvey et al[26]	2018	USA	Jan 2008-July 2017	CS	8	4 (50%)	8.2 ± 5.8	A = 1, C = 7	47.0 ± 23.9	LQTS, CPVT	NA	8/8 (100%)	β-blockers 8/8 (100%), ICD 6/8 (75%)	PP 0/8 (0%), SP 8/8 (100%)	Good
Hofferberth et al[27]	2014	USA	Aug 2000-Dec 2011	CS	22	13 (54%)	13.1 ± 7.7	A = 7, C = 16, I = 1	32.0 ± 28.8	LQTS, CPVT	518 ± 69	20/22 (92%)	β-blocker 22/22 (100%), ICD 13/22 (59%)	PP 2/22 (8%), SP 20/22 (92%)	Good
Jang et al[28]	2017	South Korea	Nov 2010-Jan 2015	CS	15	11 (73%)	24.6 ± 10.5	A = 13, C = 2	27.6 ± 11.6	LQTS, CPVT	594 ± 70	9/15 (57%)	β-blockers 15/15 (100%)	PP 6/15 (40%), SP 9/15 (60%)	Good
Li et al[29]	2005	China	2002	CS	5	3 (60%)	21.6 ± 7.0	A = 4, C = 1	21.0 ± 0.0	LQTS	590 ± 50	5/5 (100%)	β-blockers 5/5 (100%)	PP 0/5 (0%), SP 5/5 (100%)	Good
Li et al[30]	2008	China	Dec 2002-May 2007	CS	11	10 (91%)	28.5 ± 14.8	A = 9, C = 2	37.0 ± 26.3	LQTS	NA	11/11 (100%)	β-blockers 11/11 (100%)	PP 0/11 (0%), SP 11/11 (100%)	Good
Li et al[31]	2003	China	2001	CS	4	3 (75%)	32.5 ± 17.9	A = 3, C = 1	3.0 ± 0.0	LQTS	538 ± 76	4/4 (100%)	β-blockers 3/4 (75%)	PP 0/4 (0%), SP 4/4 (100%)	Good

(Continues)

TABLE 1 (Continued)

First author	Year	Country	Study period	Study type	Sample size	Female (%)	Age, y (mean ± SD)	Population: A = adults, C = children, I = infants	Time of follow-up, mo (mean ± SD)	Inherited arrhythmic disease	QTc, ms (mean ± SD)	Symptomatic before surgery, n (%)	Therapy before surgery	Indication for treatment	Quality assessment
Li et al[32]	2018	China	Nov 2007-Jan 2016	CS	8	5 (63%)	20.0 ± 8.1	A = 5, C = 3	7.0 ± 3.2	LQTS	534 ± 53	8/8 (100%)	β-blockers 8/8 (100%)	PP 1/8 (13%), SP 7/8 (87%)	Good
Marai et al[33]	2015	Israel	2010	CS	3	1 (33%)	17.3 ± 0.6	A = 1, C = 2	13.0 ± 6.2	CPVT	NA	3/3 (100%)	β-blockers 3/3 (100%), ICD 2/3 (76%)	PP 0/3 (0%), SP 3/3 (100%)	Fair
McNamara et al[34]	2017	Ireland	NA	CS	5	2 (40%)	34.2 ± 21.1	A = 3, C = 2	12.4 ± 7.4	LQTS, CPVT	NA	5/5 (100%)	β-blockers 5/5 (100%), cardiac ablation 3/5 (60%)	PP 0/5 (0%), SP 5/5 (100%)	Good
Olde Nordkamp et al[35]	2014	Netherlands	Nov 2005-Feb 2013	CS	17	10 (59%)	19.0 ± 14.0	NA	43.0 ± 49.3	LQTS, CPVT	472 ± 95	16/17 (94%)	β-blockers 17/17 (100%), ICD 8/17 (47%)	PP 1/17 (6%), SP 16/17 (94%)	Good
Ouriel et al[36]	1995	USA	Feb 1990-Aug 1993	CS	10	4 (40%)	17.1 ± 12.9	NA	15.6 ± 3.6	LQTS	520 ± 10	10/10 (100%)	β-blockers 9/10 (90%), pacemaker 4/10 (40%)	PP 1/10 (10%), SP 9/10 (90%)	Fair
Schneider et al[37]	2016	USA	Sep 2006-July 2015	CS	13	8 (62%)	21.0 ± 11.0	A, C	62.4 ± 19.2	LQTS	490 ± 47	9/13 (69%)	β-blockers 8/13 (62%), ICD 6/13 (46%)	NA	Good
Schneider et al[38]	2012	Germany	Oct 2007-Nov 2011	CS	10	3 (30%)	17.7 ± 12.3	A = 1, C = 9	27.4 ± 12.8	LQTS, CPVT	480 ± 49	10/10 (100%)	β-blockers 10/10 (100%), ICD 2/10 (20%)	PP 0/10 (0%), SP 10/10 (100%)	Good
Schwartz et al[39]	2004	Worldwide	1970-2002	CS	147	101 (69%)	17.7 ± 12.0	A, C	95.4 ± 72.0	LQTS	543 ± 65	145/147 (99%)	β-blockers 121/142 (85%), pacemaker 12/142 (8%), ICD 4/142 (3%)	PP 2/147 (1%), SP 145/147 (99%)	Good
Tarrado et al[40]	2014	Spain	2011-2013	CS	5	5 (100%)	8.8 ± 6.0	C, I	20.0 ± 10.2	LQTS, CPVT	NA	3/5 (60%)	β-blockers 3/3 (100%)	PP 2/5 (40%), SP 3/5 (60%)	Fair
Upadya et al[41]	2016	India	NA	CS	3	2 (67%)	14.0 ± 10.0	A = 1, C = 2	9.0 ± 0.0	LQTS	NA	3/3 (100%)	β-blockers 3/3 (100%)	PP 0/3 (0%), SP 3/3 (100%)	Good
Waddell-Smith et al[42]	2015	New Zealand	2008-2014	CS	47	34 (72%)	28.3 ± 47.4	A, C	32.5 ± 50.5	LQTS, CPVT	461 ± 60	25/47 (53%)	β-blockers 30/47 (64%)	PP 22/47 (47%), SP 25/47 (53%)	Good
Wilde et al[43]	2008	Worldwide	NA	CS	3	1 (33%)	17.0 ± 1.0	A = 1, C = 2	130.0 ± 105.4	CPVT	NA	3/3 (100%)	β-blockers 3/3 (100%), ICD 1/3 (33%)	PP 0/3 (0%), SP 3/3 (100%)	Good

Abbreviations: CS, case series; CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; PP, primary prevention; SP, secondary prevention.

TABLE 2 Surgical outcomes of included studies

First author	Year	Inherited arrhythmic disease	Surgical approach	Patients responsive to treatment, *n* (%)	Rate of cardiac events after surgery, *n* (%)			Rate of survival free of cardiac events after surgery, *n* (%)	QTc after surgery, ms (mean ± SD)	Rate of surgical complications, *n* (%)	
					Syncope	Aborted cardiac arrest	Sudden cardiac death			Horner syndrome	Asymmetric facial sweating
Antiel et al[17]	2016	LQTS, CPVT	VATS	NA	NA	NA	NA	NA	NA	22/61	36/60
Atallah et al[18]	2008	LQTS, CPVT	VATS	7/8	NA	NA	0/8	6/8	464 ± 78	0/9	0/9
Bos et al[19]	2013	LQTS	VATS	44/52	NA	12/52	0/52	40/52	NA	4/52	NA
Coleman et al[20]	2012	CPVT	VATS	18/18	NA	2/18	0/18	16/18	NA	3/18	NA
Collura et al[21]	2009	LQTS, CPVT	VATS (18/20)	16/18	0/18	2/18	0/18	16/18	508 ± 62	0/18	0/18
			Open (2/20)	2/2	0/2	1/2	0/2	1/2		0/2	0/2
Costello et al[22]	2015	LQTS, CPVT	VATS (10/10)	7/10	1/10	2/10	0/10	7/10	469 ± 41	0/10	4/10
De Ferrari et al[23]	2015	CPVT	VATS (29/63)	50/63	1/63	13/63	1/63	50/63	NA	0/63	0/63
			Open (34/63)								
Desimone et al[24]	2015	LQTS, CPVT	VATS	NA	NA	NA	NA	55/72	491 ± 40	NA	NA
Epstein et al[25]	1996	LQTS	Open	5/5	0/5	0/5	0/5	3/5	532 ± 108	0/5	NA
Garvey et al[26]	2018	LQTS, CPVT	VATS	6/8	NA	NA	0/8	NA	NA	2/8	1/8
Hofferberth et al[27]	2014	LQTS, CPVT	VATS	16/22	NA	5/22	0/22	12/22	504 ± 46	0/22	NA
Jang et al[28]	2017	LQTS, CPVT	VATS	13/15	1/15	1/15	0/15	13/15	579 ± 69	0/15	15/15
Li et al[29]	2005	LQTS	Open	4/5	1/5	0/5	0/5	4/5	480 ± 40	0/5	NA
Li et al[30]	2008	LQTS	VATS	9/11	2/11	0/11	1/11	7/11	NA	0/11	NA
Li et al[31]	2003	LQTS	VATS	4/4	0/4	0/4	0/4	4/4	512 ± 57	0/4	NA
Li et al[32]	2018	LQTS	VATS	8/8	4/8	4/8	0/8	4/8	486 ± 35	0/8	0/8
Marai et al[33]	2015	CPVT	Open	0/3	3/3	0/3	0/3	0/3	NA	1/3	NA
McNamara et al[34]	2017	LQTS, CPVT	VATS	4/5	0/5	0/5	1/5	4/5	NA	1/5	NA
Olde Nordkamp et al[35]	2014	LQTS, CPVT	Open (7/17)	14/16	NA	NA	1/17	8/16	481 ± 82	1/17	1/17
			VATS (10/17)								
Ouriel et al[36]	1995	LQTS	Open	9/10	1/10	0/10	1/10	9/10	490 ± 10	9/10	NA
Schneider et al[37]	2016	LQTS	Open	10/13	NA	3/13	0/13	10/13	451 ± 34	NA	NA
Schneider et al[38]	2012	LQTS, CPVT	Open	10/10	1/10	0/10	0/10	9/10	473 ± 43	1/10	NA
Schwartz et al[39]	2004	LQTS	Open	93/147	46/147	24/147	10/147	67/147	504 ± 11	NA	NA
Tarrado et al[40]	2014	LQTS, CPVT	VATS	5/5	0/5	0/5	0/5	5/5	NA	0/5	0/5
Upadya et al[41]	2016	LQTS	VATS	3/3	0/3	0/3	0/3	3/3	NA	NA	NA
Waddell-Smith et al[42]	2015	LQTS, CPVT	VATS	47/47	5/47	0/47	0/47	42/47	476 ± 54	9/47	27/47
Wilde et al[43]	2008	CPVT	Open	3/3	0/3	0/3	0/3	3/3	NA	NA	NA

Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; VATS, video-assisted thoracoscopic surgery.

maximum tolerated dose at the time of LCSD (513/578, 88.8%) and an ICD was implanted in 161/533 (30.2%). The main indication for LCSD was secondary prevention (495/632, 78.3%) and the mean age at LCSD was 18.3 ± 13.9 years. The surgical technique was thoracoscopic in 408/647 (63.1%) and open in 239 (36.9%). Patients were observed for a mean follow-up of 32.3 ± 32.5 months.

Fourteen studies had a sample size ≥10 and 507/647 patients (78.4%) were therefore included in the meta-regression.[17,19-22,24,27,28,30,36-39,42] The VATS approach was used in 10 studies, 327/507 patients (64.5%), and the open approach in 4, 180/507 patients (35.5%). Baseline characteristics of the studies included in the meta-regression are depicted in Table 3. The results of the meta-regression are shown in Table 4.

3.2 | Patients' responsiveness to treatment

Twenty-five studies included data regarding the number of patients responsive to treatment and 357/511 (69.9%) were identified as responsive to the surgical procedure. Of these, 12 papers had a sample size ≥10 and were included in the quantitative synthesis. In the VATS and open groups, 170/193 patients (88.1%) and 122/180 (67.8%), respectively, experienced less life-threatening CEs after LCSD. Meta-regression demonstrated no difference in responsiveness to treatment between the VATS and open approaches (β-coefficient 2.75, 95% CI −2.85 to 8.35, P = .336, I^2 = 89.09%).

3.3 | Patients symptomatic before vs postsurgery

Twenty-five studies included data regarding the number of patients with CEs before and after surgery. Overall, 473/585 (80.9%) were symptomatic before treatment and 187/585 (32.0%) after treatment. Thirteen articles met the meta-regression inclusion criterion. In the meta-regression, patients symptomatic before and after surgery were 172/265 (64.9%) and 57/265 (21.5%) in the VATS group vs 174/180 (96.7%) and 85/180 (47.2%) in the open group. One approach did not provide an advantage over the other in terms of the likelihood of being asymptomatic after surgery (β-coefficient −1.26, 95% CI −6.25 to 3.72, P = .619, I^2 = 85.45%).

3.4 | QTc before vs postsurgery

Sixteen studies reported the mean QTc before and after surgery for LQTS patients, which was 522 ± 61.6 ms before surgery and 494 ± 52.3 ms after surgery. Ten studies were included in the meta-regression. When thoracoscopic and open surgery were compared, the mean QTc before and after surgery was 511 ± 61.3 ms vs 503 ± 51.5 ms in the VATS group, and 508 ± 47.3 ms vs 480 ± 28.4 ms in the open group. Patients operated with the VATS approach had a significantly smaller shortening of QTc duration (β-coefficient −20.04, 95% CI −36.82 to −3.27, P = .019).

3.5 | Patients free from CEs after surgery

Twenty-five studies included data regarding the number of patients free from CEs after surgery. Overall, at the end of the follow-up period, 398/585 patients (68.0%) were free from CEs. Thirteen studies were included in the quantitative synthesis. In the VATS group, 208/265 patients (78.5%) had a postoperative period free of cardiac event vs 95/180 (52.8%) in the open group. Patients who underwent VATS did not have a higher likelihood of being free from CEs during the follow-up period (β-coefficient 4.55, 95% CI −2.08 to 11.18, P = .178, I^2 = 93.04%).

3.6 | Syncope episodes after surgery

Eighteen studies included data regarding the number of patients experiencing syncope episodes after surgery and 66/374 patients (17.6%) had one or more episodes. Of these, eight papers were included in the meta-regression. The event rate of one or more syncope episodes in the postoperative period was 9/101 (8.9%) in the VATS group and 48/167 (28.7%) in the open group. There was no detectable difference in the number of patients experiencing syncope episodes between the VATS and open approaches (β-coefficient −1.39, 95% CI −3.84 to 1.06, P = .268, I^2 = 87.06%).

3.7 | ACA after surgery

Twenty-two studies included data regarding the number of patients experiencing ACA after surgery and 69/479 patients (14.4%) had one or more episodes. Twelve papers were included in the quantitative synthesis. In the VATS group, 24/193 patients (12.4%) had one or more ACAs vs 27/180 (15.0%) in the open group. Meta-regression demonstrated that there was no difference in the number of patients experiencing ACAs between the VATS and open approaches (β-coefficient .09, 95% CI −1.22 to 1.41, P = .89, I^2 = 80.94%).

3.8 | SCD after surgery

Twenty-five studies included data regarding the number of SCD after surgery and 15/512 patients (2.9%) died of SCD during the follow-up. Twelve papers were included in the quantitative synthesis. One patient out of 193 (0.5%) died of SCD in the VATS group vs 11/180 (6.1%) in the open group. No difference in the number of SCDs between the two groups was found (β-coefficient −.02, 95% CI −0.34 to 0.30, P = .894, I^2 = 1.15%).

3.9 | Horner's syndrome

Twenty-two studies included data regarding the number of patients that were diagnosed with either transient or persistent Horner's syndrome after surgery and 53/408 patients (13.0%) developed Horner's syndrome during the follow-up. Ten studies had a sample size ≥10 and were included in the quantitative synthesis. A diagnosis of Horner's syndrome was made in 38/254 patients (15.0%) operated with VATS and in 10/20 (50.0%) operated with an open approach. No difference in the number of patients diagnosed with Horner's syndrome between the two groups was identified (β-coefficient −.003, 95% CI −0.013 to 0.007, P = .563, I^2 = 94.94%).

TABLE 3 Baseline characteristics and surgical outcomes of studies included in the meta-regression analysis grouped by operative approach

	VATS (*n* = 10)	Open (*n* = 4)
No. patients, *n* (%)	327/507 (64.5%)	180/507 (35.5%)
LQTS, *n* (%)	272/318 (85.5%)	175/180 (97.2%)
CPVT, *n* (%)	46/318 (14.5%)	5/180 (2.8%)
Age at surgery, years (mean ± SD)	17.7 ± 18.0	18.4 ± 12.1
Medical therapy before surgery (β-blockers), *n* (%)	231/265 (87.1%)	148/175 (84.6%)
Indication for surgery, *n* (%)	Primary: 123/327 (37.6%)	Primary: 3/167 (1.8%)
	Secondary: 204/327 (62.4%)	Secondary: 164/167 (98.2%)
Follow-up, months (mean ± SD)	28.4 ± 26.5	50.2 ± 37.8
Symptomatic before surgery, *n* (%)	172/265 (64.9%)	174/180 (96.7%)
Symptomatic after surgery, *n* (%)	57/265 (21.5%)	85/180 (47.2%)
QTc before surgery, ms (mean ± SD)	511 ± 61.3	508 ± 47.3
QTc after surgery, ms (mean ± SD)	503 ± 51.5	480 ± 28.4
Patients responsive to treatment, *n* (%)	170/193 (88.1%)	122/180 (67.8%)
Post-op syncope, *n* (%)	9/101 (8.9%)	48/167 (28.7%)
Post-op aborted cardiac arrest, *n* (%)	24/193 (12.4%)	27/180 (15.0%)
Post-op sudden death, *n* (%)	1/193 (0.5%)	11/180 (6.1%)
Survival free of cardiac events after surgery, *n* (%)	208/265 (78.5%)	95/180 (52.8%)
Post-op Horner's syndrome, *n* (%)	38/254 (15.0%)	10/20 (50.0%)
Post-op asymmetric facial sweating, *n* (%)	82/150 (54.7%)	NA

Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; VATS, video-assisted thoracoscopic surgery.

3.10 | Asymmetric facial sweating

Eleven studies included data regarding the number of patients that developed asymmetric facial sweating after surgery and 84/262 patients (32.1%) developed asymmetric facial sweating during the follow-up. Five studies were included in the quantitative synthesis and all belonged to the VATS group: 82/150 patients (54.7%) operated on with VATS LSCD developed asymmetric facial swelling postoperatively (β-coefficient 6.24, 95% CI 2.01 to 10.46, P = .004, I^2 = 91.21%). A comparison between the two approaches was not possible because no studies with a sample size ≥10, and that used an open surgery approach, reported data on this variable.

4 | COMMENT

The management of LQTS, CPVT patients who continue to have CEs despite maximal medical therapy is complex. LCSD has proven to be an additive treatment option for patients with potentially life-threatening channelopathies given its antifibrillatory effect.[23,39] The purpose of this meta-analysis was to assess the long-term outcomes of LCSD for LQTS, CPVT patients. We also aimed to investigate whether there was any significant difference in outcomes between the VATS and open approaches.

4.1 | Rationale and mechanism of action of LCSD

Multiple mechanisms have been identified at the basis of the antiarrhythmic and antifibrillatory effect of LCSD.[11] This is mainly due to its antiadrenergic effect at the ventricular levels, therefore preventing early afterdepolarizations and re-entry mechanisms.[44,45] Thus, LCSD has been introduced in the clinical practice as a therapeutic measure used in high-risk LQTS/CPVT patients to decrease the risk of CEs, especially in those refractory to maximal medical therapy. The findings of our meta-regression reinforce the concept that life-threatening arrhythmias might be prevented or reduced by LCSD.

4.2 | LCSD and CEs

More than two thirds of LQTS/CPVT patients 357/511 (69.9%) experienced a reduction in the number of CEs after surgery. Although this technique decreases the risk of CEs (80.9% presurgery vs 32.0% postsurgery), it does not eliminate it and some patients still experienced life-threatening arrhythmias during the follow-up. However, in some high-risk patients and in those who have several ICD discharges while being treated with β-blockers and an ICD, the decline in the number of CEs carries strong implications in terms of quality of life. Previous studies have proved this in their LQTS/CPVT cohorts undergoing LCSD as the majority of their patients were happy with the procedure and felt safer.[17,42] From our findings, both approaches appeared to be equally effective in reducing the occurrence of CEs in the postoperative period.

4.3 | LCSD and the QT interval

LCSD shortened QTc duration in LQTS patients from 522 ± 61.6 ms to 494 ± 52.3 ms. Thus, LCSD seems to have a positive action also

TABLE 4 Results of the meta-regression analysis

Variable	No. studies	Sample size	Coefficient (95% CI)	Standard error	*P* value	I^2 (%)
Symptomatic after surgery						
Open	4	180	−6.57 (−10.66 to −2.48)	2.09	.002	85.45
VATS	9	265	−1.26 (−6.25 to 3.72)	2.55	.619	
Responsiveness to treatment						
Open	4	180	6.15 (1.66 to 10.64)	2.29	.007	89.09
VATS	8	193	2.75 (−2.85 to 8.35)	2.86	.336	
Post-op syncope						
Open	3	167	2.19 (0.25 to 4.14)	0.99	.027	87.06
VATS	5	101	−1.39 (−3.84 to 1.06)	1.25	.268	
Post-op aborted cardiac arrest						
Open	4	180	0.96 (−0.07 to 1.99)	0.52	.067	80.94
VATS	8	193	0.09 (−1.22 to 1.41)	0.67	.89	
Post-op Horner's syndrome						
Open	2	20	0.007 (−0.002 to 0.016)	0.005	.15	94.94
VATS	9	254	−0.003 (−0.013 to 0.007)	0.005	.563	
Post-op asymmetric facial sweating						
Open	0	0	–	–	–	91.21
VATS	5	150	6.24 (2.01 to 10.46)	2.15	.004	
Post-op sudden cardiac death						
Open	4	180	0.24 (0.0006 to 0.47)	0.12	.049	1.15
VATS	8	193	−0.02 (−0.34 to 0.30)	0.16	.894	
Survival free of cardiac events after surgery						
Open	4	180	5.24 (−0.20 to 10.68)	2.77	.059	93.04
VATS	9	265	4.55 (−2.08 to 11.18)	3.38	.178	
Post-op QTc change						
Open	4	180	28.39 (15.36 to 41.43)	6.65	<.0001	NA
VATS	6	184	−20.04 (−36.82 to −3.27)	8.56	.019	

Abbreviations: CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

on the arrhythmogenic substrate represented by QT interval duration. Since patients with a QTc ≥500 ms are associated with lower event-free survival rates and a higher yearly rate of SCD,[39] LCSD could have a protective effect not only by interfering with the release of norepinephrine, but also by reducing the duration of the QT interval. Open surgery was associated with a significant greater reduction in QTc (508 ± 47.3 vs 480 ± 28.4) with respect to VATS (511 ± 61.3 vs 503 ± 51.5). This might be due to the longer duration of the follow-up period in the open group (50.2 ± 37.8 months vs 28.4 ± 26.5 months) or to the surgical technique itself.

4.4 | Surgical complications

Potential surgical complications of LCSD are Horner's syndrome and asymmetric facial sweating, whose incidences have been estimated by our analysis to be 13.0% and 32.1%, respectively. This indicates how the side effects of LCSD are not minimal as suggested by previous studies,[8] even though they are likely outweighed by the benefits, and warrants a counseling comprehensive of surgical complications for patients undergoing this treatment. The low number of papers that reported the occurrence of such complications has hindered the comparison between the two approaches. Future studies should focus more on the surgical side effects as not reporting them might lead to an underestimation of their entity.

4.5 | Study limitations

This meta-analysis examined retrospective case series with variable sample size and follow-up. Due to the intrinsic nature of case series, potential bias exists in the selection on patients for LCSD. Due to the rarity of the disease and the superiority of the medical therapy, a randomized controlled trial comparing VATS and open approaches has never been conducted. With all included studies being case series, our study lacked a true control group, hindering therefore the outcomes of our analysis. The inclusion of old studies in the analysis might have negatively affected the results due

to the evolution of surgical techniques and tools over the years. Due to none of the analyzed studies reporting data on the short-term surgical outcomes not LCSD related, it was not possible to conclude which approach is associated with a lower occurrence of side effects such as pain, pulmonary complications, bleeding or subcutaneous emphysema, and to a reduced length of hospital stay. A reporting bias was also observed for the patients' baseline characteristics, surgical outcomes and side effects related to LCSD. Standardized reporting guidelines for patients undergoing LCSD could ensure that future studies include all relevant preoperative and postoperative details.

5 | CONCLUSIONS

After LCSD the majority of LQTS/CPVT patients seems to remain free of CEs. In patients who continue to experience CEs, LCSD, even without affording 100% protection, may reduce the number of CEs. In LQTS patients, LSCD seems to be associated with a shortening of the QTc interval. Compared to traditional LCSD, VATS does not seem to offer a safer and more effective treatment option. Due to the limitations that hindered our study, a randomized trial is warranted to fully establish the safety and efficacy of LCSD.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors contributed to writing this paper.
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