Left cardiac sympathetic denervation and device implantation in congenital long QT syndrome – A case series and review.

Mohammed Sameer[1], Sabarinath Menon[1], Baiju Sasi Dharan[1], and Narayanan Namboodiri[1]

[1]Sree Chitra Tirunal Institute for Medical Sciences and Technology

January 17, 2022

Abstract

Introduction and aim of the study: Long QT syndrome is a life threatening genetic arrhythmia syndrome which is characterized by ventricular arrhythmias with few children often having their initial clinical presentation as sudden cardiac arrest. This condition poses a very high risk of sudden death demanding proper management of such children. Many treatment modalities are available in this era, with each one of them carrying advantages and disadvantages. **Materials and methods:** We present a series of four children suffering from Long QT syndrome, who were successfully managed with left cardiac sympathetic denervation (LCSD) combined with device implantation (permanent pacemaker implantation in two children and implantable loop recorder in one child). **Results:** All four children are asymptomatic since hospital discharge with no episodes of syncope or presyncope, or device-detected ventricular tachyarrhythmia till to-date. **Conclusion:** Left cardiac sympathetic denervation is an underutilized simple surgical procedure, for Long QT syndrome. When combined with other treatment strategies (like device implantation in our case series), outcome is far better than a single technique. Beta-blockers play a very important role both in pre-operative and immediate post-operative period and have to be continued for the rest of life.

TITLE PAGE

Title : Left cardiac sympathetic denervation and device implantation in congenital long QT syndrome – A case series and review.

Short running title : Left cardiac sympathetic denervation

Authors: Mohammed Sameer[1] M.Ch, Sabarinath Menon[1*] M.Ch, Baiju Sasi Dharan[1]M.Ch, Narayanan Namboodiri[2] D.M.

Department of Cardiovascular and Thoracic surgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Professor, Department of Cardiology and Electrophysiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

***Corresponding Author:**

Dr. Sabarinath Menon, MBBS, MS, MCh,

Additional Professor, Congenital heart surgery unit,

Department of Cardio Vascular and Thoracic Surgery,

Sree Chitra Tirunal Institute for Medical Sciences and Technology,

Thiruvananthapuram-695011, Kerala, India.

Ph: +91-999584442.

E-mail: sabarinath.menon@gmail.com.

Data availability statement: Available

Funding statement: No source of funding was provided for the study.

Conflict of interest disclosure: None declared

Institutional Review Board approval or waiver: Not applicable

Patient consent statement: Informed oral consent was obtained.

Permission to reproduce material from other sources: Yes

Clinical trial registration: N/A

Abstract

Introduction and aim of the study: Long QT syndrome is a life threatening genetic arrhythmia syndrome which is characterized by ventricular arrhythmias with few children often having their initial clinical presentation as sudden cardiac arrest. This condition poses a very high risk of sudden death demanding proper management of such children. Many treatment modalities are available in this era, with each one of them carrying advantages and disadvantages.

Materials and methods: We present a series of four children suffering from Long QT syndrome, who were successfully managed with left cardiac sympathetic denervation (LCSD) combined with device implantation (permanent pacemaker implantation in two children and implantable loop recorder in one child).

Results: All four children are asymptomatic since hospital discharge with no episodes of syncope or presyncope, or device-detected ventricular tachyarrhythmia till to-date.

Conclusion: Left cardiac sympathetic denervation is an underutilized simple surgical procedure, for Long QT syndrome. When combined with other treatment strategies (like device implantation in our case series), outcome is far better than a single technique. Beta-blockers play a very important role both in pre-operative and immediate post-operative period and have to be continued for the rest of life.

Key words: Long QT syndrome, left cardiac sympathetic denervation, permanent pacemaker, sudden cardiac death.

Main Text

Introduction:

Long QT syndrome is characterized by life threatening ventricular arrhythmias, and even sudden cardiac arrest (SCA) as the initial clinical presentation. High risk of SCA at young age demands focused management of the children affected with this genetic arrhythmia syndrome. Many treatment options are available for the management of this condition, with a goal to prevent SCA. We present a series of patients who were managed with left cardiac sympathetic denervation (LCSD) combined with device implantation (permanent pacemaker implantation in two children and implantable loop recorder in one child).

Materials and Methods :

An institutional review board waiver was obtained to perform the study. A formal informed oral consent was obtained from the parents of children for the purpose of this study. An ethics approval statement was not requiring, as IRB waiver was obtained. All the data was obtained from the inpatient and outpatient records and recent follow-up data was collected over the phone.

Case 1:

A 3 year 7-month-old girl, 2nd in birth order had fetal bradycardia but no distress during antenatal period. Immediate post-natal period was uneventful with low heart rate with varying T wave morphology. Holter study reported as prolonged QT with T wave alternans (TWA) throughout study and Brain Stem Evoked Response Audiometry (BERA) revealed mild bilateral hearing loss. Child had poor weight gain with large patent ductus arteriosus (PDA) on echo. There was no family history of syncope or SCA and prolonged QTc in parents or elder sibling. Attempted device closure of PDA was aborted due to ventricular tachycardia (VT) and brief period of arrest – Torsade's de pointes (TDP) during the procedure and rhythm reverted by DC version. She was started on high dose propranolol and planned for further management. As the TWA persisted (Figure.1) and she had to undergo PDA closure or ligation, an alternate strategy was planned. She underwent PDA ligation, left cardiac sympathetic denervation (T2-5) with epicardial lead placement through left posterolateral thoracotomy. Post-operatively, specific T wave pattern with reduced QTc interval was observed (Figure.2).

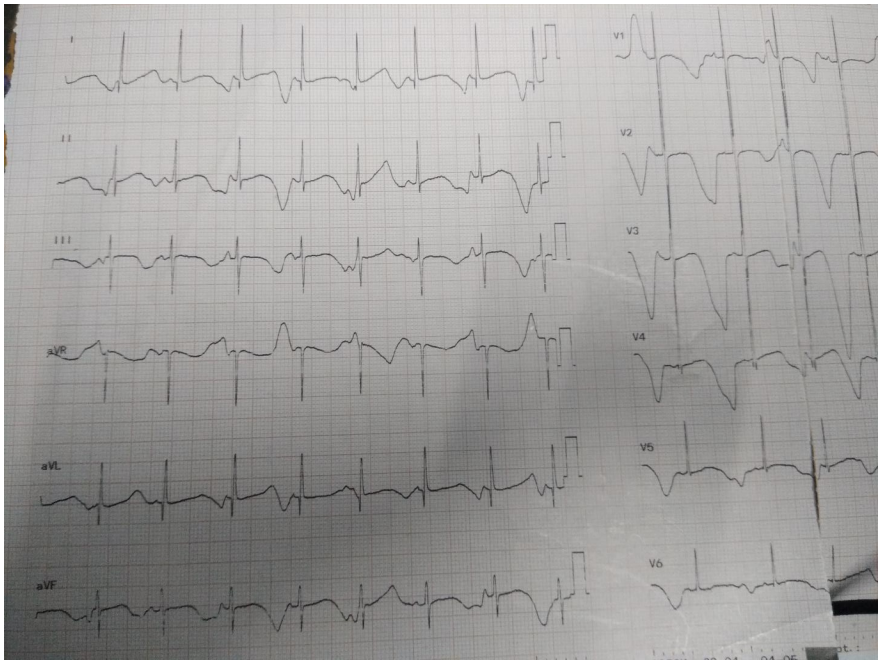

Figure.1: Pre-operative ECG showing prolonged QTc with T-wave alternans.

Figure.2: Post-operative ECG showing monomorphic T-wave with loss of TWA. TWA – T wave alternans.

Case.2:

A 3 year 2-month-old boy, 2nd in birth order had uneventful antenatal and immediate post-natal period. Elder sibling had deafness with seizures and sustained sudden cardiac death before 6 months of age without being diagnosed. Mother also has prolonged QTc 560 m sec. In view of strong family history, BERA revealed severe bilateral sensorineural hearing loss with long QT syndrome. Echo revealed structurally normal heart. Child was started on high-dose propranolol, despite that he had syncopal episodes with occasional seizures. He underwent LCSD (T2-3) through left posterolateral thoracotomy. Post-operatively, reduction in QTc interval was noted with persistent TWA.

Variables	Case.1
Age (in months)	43
Gender	Female

Variables	Case.1
Presenting complaint	Neonatal ECG (Bradycardia with varying T morph
Sudden cardiac arrest	Yes
Congenital sensorineural hearing loss	Yes
QTc interval	550 ms
Family history	No
Modified Schwartz criteria score	7
Echocardiography	PDA
Pre-operative β-blocker	Yes
Symptom status on β-blocker	No
Significant events	VT during PDA device closure
Level of sympathetic denervation (Lower half of stellate ganglion till)	T5
Additional procedure	PDA ligation
Approach	Left posterolateral Thoracotomy
Pacing intervention	Epicardial: Single chamber
Follow-up	Asymptomatic

ECG-Electrocardiogram, ILR-Implantable Loop Recorder, PDA-Patent ductus arteriosus, VT-Ventricular tachycardia.

Table 1: Clinical features of patients who underwent LCSD

Case.3:

A 3 year 4-month-old boy, 2^{nd} in birth order with uneventful antenatal and immediate post-natal period. He had recurrent episodes of syncopal attacks without seizures for 3 months of age lasting for 2-3 min with spontaneous recovery (Total 7 episodes). Mother has prolonged QTc interval. Elder sibling is healthy. He was evaluated for syncope under Neurology and EEG was reported normal. He also has delayed speech milestones and recently detected hearing loss. ECG revealed prolonged QTc (670 ms) with T wave alternans (Figure.3). He was immediately started on propranolol and developed significant bradycardia. Hence, he subsequently underwent left cardiac sympathetic denervation and PPI through left posterolateral thoracotomy.

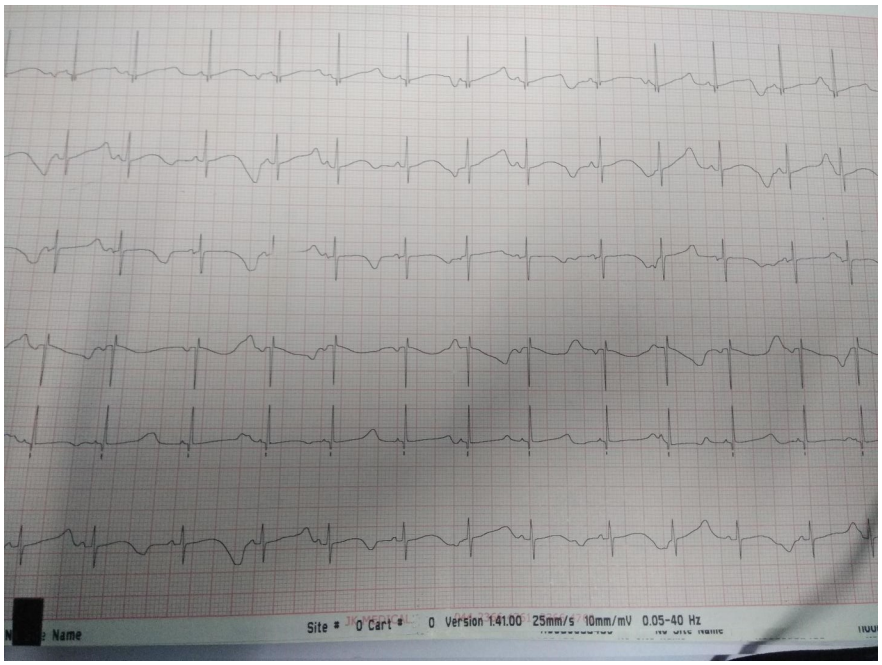

Figure.3: Pre-operative ECG showing prolonged QTc interval with TWA and varying R-R interval.

Variable	Case.1	Case.2	Case.3	Case.4
QTc interval	3	3	3	3
Syncope	-	2	2	2
TDP	2	-	-	-
TWA	1	1	1	-
Congenital deafness	0.5	0.5	0.5	0.5
Low heart rate	0.5	0.5	-	-
SCD in family	-	0.5	-	-
Total score	7	7.5	6.5	5.5

LQTS-Long QT syndrome, SCD-Sudden cardiac death, TDP-Torsade's de pointes, TWA-T wave alternans. QTc interval [?] 480 ms: 3[1]. Score [?] 3.5 indicates high probability of Long QT syndrome.

Table 2: Probabilistic score based on Modified Schwartz's criteria[2].

Case.4:

A 2 year 8-month-old boy, 3rd in birth order with uneventful antenatal and immediate post-natal period presented with recurrent episodes of syncopal attacks and an episode of unresponsiveness with successful resuscitation. He had congenital bilateral sensorineural hearing loss and underwent cochlear implantation. Father and two older siblings have prolonged QTc interval ($>$ 450 ms). He was diagnosed to have long QT syndrome and underwent LCSD and implantable loop recorder through left posterolateral thoracotomy.

Technique of Left Cardiac Sympathetic Denervation (LCSD):

All children were operated under general anesthesia in left lateral position. Muscle sparing left posterolateral thoracotomy was performed through 3rd or 4th intercostal space. Pleura was opened and lung was retracted to expose the posterior mediastinal pleura. Descending thoracic aorta is identified. A small incision is placed

just lateral to the aorta in the pleura at the level of crossing of 1st superior intercostal vein. Chain of thoracic sympathetic ganglia are identified along with stellate ganglion (Fused ganglion of lower cervical and upper T1 ganglia). Chain is exposed till T4 or T5 (Fig.4). Left cardiac sympathetic denervation is performed by removing lower half of stellate ganglion and upper thoracic ganglia (T1-T4/5). Excised nerve tissue is sent for histopathology for confirmation.

Posterior mediastinal pleura is loosely approximated. One child had additional PDA which was ligated. Pericardium is opened at the anterior border and epicardial pacing leads were placed and pulse generator was positioned in the pleural cavity by suturing it to the thoracic wall. Thoracotomy is closed in a usual layered manner after placing left pleural drain. Patients are usually weaned early and extubated within few hours after shifting to the intensive care unit.

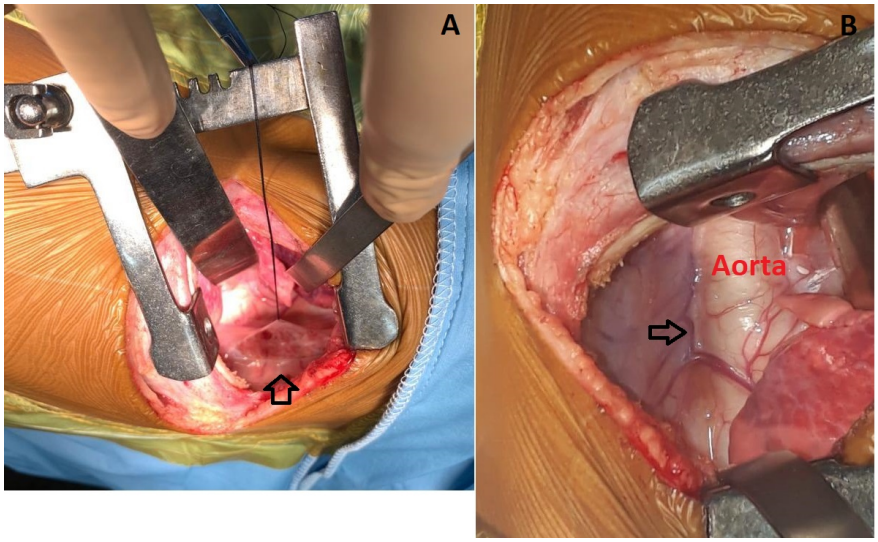

Figure.4: Surgical technique of left cardiac sympathetic denervation by left posterolateral sympathectomy. **Image. A** show reflected posterior parietal pleura with black arrow pointing to left sympathetic chain. **Image. B** shows relationship of sympathetic chain with descending thoracic aorta.

All four children had uneventful postoperative stay in ICU and ward, except case.3 who developed post-operative TDP. This child was not reinitiated on beta-blockers immediately after the procedure and hence predisposed him to develop TDP. Later, he was managed with intravenous loading dose followed by oral maintenance beta blockers, which prevented further episodes. Case.1 and Case.4 had immediate reduction in TWA before discharge from the hospital. All the four children are healthy and alive without any symptoms till date on latest follow-up.

Discussion:

Long QT syndrome can be congenital or acquired. Congenital long QT syndrome is associated with refractory ventricular arrhythmias, Torsade de pointes, ventricular fibrillation and even sudden cardiac death. Among the various options available to prevent sudden cardiac death, beta-blocker therapy is the first-line mainstay treatment[3]. However, not all patients respond to this treatment and responders still carry risk of sudden cardiac death[4]. In those patients who are intolerable or refractory, other options include LCSD), permanent pacemaker insertion and Implantable Cardioverter Defibrillator (ICD) implantation[5].

Although every management is associated with its own risks and benefits, currently ICD implantation is widely accepted as an adjuvant to beta-blocker therapy. However, ICD implantation is suitable mainly in high-risk adult patients. ICD implantation in pre pubertal, young and active patients is associated with device malfunction (inappropriate shocks), infection and psychological problems [6]. Furthermore, it

necessitates life-long and routine device replacement in young patients. The efficiency of ICD is further limited to its ineffectiveness in terminating tachyarrhythmias of polymorphic ventricular tachycardia (VT), bidirectional VT, and electrical storm[7]. Availability of appropriate size AICD is another concern in pediatric patients. Frequent shocks can initiate hyperadrenergic storm, and can lead on to VT storm. Many episodes of TDP could be self-terminating, but may be subjected to cardioversion.

The other treatment options in these subsets of patients include LCSD and pacemaker implantation which have been studied earlier and proved their efficacy in reducing the number of significant events culminating in death. Whatever may be the form of treatment, beta-blockers are must as they prevent the development of torsades by reducing the heart rate, shortening QT and sympatholysis. Hence, decisions regarding the correct course of treatment are consequently challenging [8].

LCSD is a well-established procedure with large and multicentric studies reporting consistent efficacy in reducing cardiac events, albeit it's an underutilized technique [8]. Its main applications are in those children with β-blocker intolerance or refractoriness, high risk of sudden death on β-blockers, frequent ICD shocks, as a bridge to ICD implantation in infants and small children[9,10]. In such patients, asynchronous cardiac sympathetic denervation and ventricular refractoriness will prevent the occurrence of torsade's[11]. LCSD prevents norepinephrine release in the heart and raises the threshold for ventricular fibrillation without impairing myocardial contractility or reducing heart rate[12,13]. It is especially effective in patients with poor compliance to β-blockers. Also, reduces the number of shocks in patients with frequent shocks thereby improving quality of life.

Surgical techniques for LCSD :

Left stellectomy and left cervicothoracic sympathectomy were two initially described techniques of LCSD. These techniques were associated with Horner's syndrome and hence high thoracic left sympathectomy was introduced. In this lower half of the stellate ganglion and the first four or five left thoracic sympathetic ganglia are removed. Resection of the lower half of the stellate ganglion is considered necessary for the anti-fibrillatory effect [10].

Conventional approaches include left posterolateral thoracotomy, supraclavicular extra pleural approach. Both the approaches carry same risks; however, thoracotomy was preferred in our institute as it resulted in completeness of surgical procedure, access and moreover in infants, it is preferred technique. We have also placed epicardial permanent pacemaker in these patients. Recently developed technique was VATS – LCSD which employs minimally invasive video thoracoscopic techniques to perform LCSD [14]. Even though, various benefits of VATS-LCSD are established over conventional thoracotomy, its role in small children and in conjunction with epicardial PPI remains to be well documented [15].

In the largest series of LCSD in long QT syndrome patients, 46% of patients were asymptomatic, with cardiac event rate dropped by 91%. Also observed was reduction in the number of shocks experienced by 95%[16]. In the recent guidelines, it has been recommended to perform LCSD as class I and IIa indication[17]. Although majority of studies reported decrease in the number of cardiac events, 20-50% remain symptomatic. Hence, LCSD should be considered as an event-attenuating procedure, and should not be viewed as curative or alternative to ICD placement.

Pacemaker therapy has a complementary role, at least theoretically, when used along with LCSD in children. QTc shortens further on high heart rate. LGL phenotype is known to have sinus bradycardia,[18] and two of our cases had low heart rate. This gets more pronounced with addition of beta blockers. Last but not the least, these devices can reliably identify the cardiac rhythm during future episodes of syncope, if any, and guide further therapy in them. The importance of pacing therapy is being relooked recently with available mounting evidence [19,20]

Hence, in patients where ICD implantation is not an optimal therapy possible (reasons provided earlier), epicardial PPI is an effective alternative. The beneficial effects of pacing in high-risk LQTS patients probably relate to the prevention of bradycardia, pauses, and the shortening of long QT intervals -factors that are

known to be arrhythmogenic in this syndrome [3]. Permanent cardiac pacing reduces the rate of recurrent syncopal events in high-risk LQTS patients, but it does not provide complete protection. It's called as anti-bradycardia pacing [21]. Permanent pacing may be efficacious by decreasing the dispersion of refractoriness.

The efficacy of LCSD should be judged only on the development of symptoms or cardiac events during the follow-up period. Patients with only syncope and a post-LCSD QTc $<$ 500ms were at a very low risk of adverse events [11].

In patients with LQTS, episodes of torsade's de pointes are usually adrenergic dependent, but spontaneous or beta-blocker-induced bradycardia may act as a provocative agent for episodes of torsade de pointes in these patients[22]. Permanent pacing plays an obvious role in alleviating bradycardia-related symptoms induced by beta-blocking drugs. Hence, permanent pacing and beta-blocker therapy can control these arrhythmias.

In our series, three management strategies were employed to control arrhythmias and to bridge for ICD implantation later in their life post pubertal age. All our patients were on β-blocker therapy pre-operatively, and continued to develop symptoms despite therapy. All the patients were offered LCSD and additional procedure of epicardial PPI in high-risk patients (two children) and Implantable Loop recorder in borderline high-risk patient (one child). Even post-operatively, β-blocker has to be initiated as early as possible. In our series, patient two developed ventricular tachycardia and impending arrest in the immediate post-operative due to late re-introduction of β-blocker, which reflects its importance. This combination prevents adrenergic dependent torsade's, β-blocker therapy reduces heart rate and PPI helps in preventing bradycardia induced torsades and also pauses. Altogether, there will be significant decrease in cardiac events till bridge to ICD implantation if deemed necessary.

All four children are asymptomatic since hospital discharge with no episodes of syncope or presyncope, or device-detected ventricular tachyarrhythmia.

Bibliography:

1. Schwartz PJ, Crotti L, Insolia R. Long-QT Syndrome. *Circ Arrhythm Electrophysiol* . 2012;5(4):868-877. doi:10.1161/CIRCEP.111.962019

2. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J* . 2013;34(40):3109-3116. doi:10.1093/eurheartj/eht089

3. Moss Arthur J., Zareba Wojciech, Hall W. Jackson, et al. Effectiveness and Limitations of β-Blocker Therapy in Congenital Long-QT Syndrome. *Circulation* . 2000;101(6):616-623. doi:10.1161/01.CIR.101.6.616

4. Schwartz Peter J., Spazzolini Carla, Priori Silvia G., et al. Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them? *Circulation* .2010;122(13):1272-1282.

5. Hocini M, Pison L, Proclemer A, et al. Diagnosis and management of patients with inherited arrhythmia syndromes in Europe: results of the European Heart Rhythm Association Survey. *Europace* . 2014;16(4):600-603. doi:10.1093/europace/euu074

6. Miyake Christina Y., Webster Gregory, Czosek Richard J., et al. Efficacy of Implantable Cardioverter Defibrillators in Young Patients With Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ Arrhythm Electrophysiol* . 2013;6(3):579-587.

7. Marai I, Khoury A, Suleiman M, et al. Importance of Ventricular Tachycardia Storms Not Terminated by Implantable Cardioverter Defibrillators Shocks in Patients With CASQ2 Associated Catecholaminergic Polymorphic Ventricular Tachycardia. *Am J Cardiol* . 2012;110(1):72-76. doi:10.1016/j.amjcard.2012.02.049

8. Cho Y. Left cardiac sympathetic denervation: An important treatment option for patients with hereditary ventricular arrhythmias. *J Arrhythmia* . 2016;32(5):340. doi:10.1016/j.joa.2015.08.002

9. Schwartz P J, Locati E H, Moss A J, Crampton R S, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. A worldwide report. *Circulation* . 1991;84(2):503-511. doi:10.1161/01.CIR.84.2.503

10. Schwartz Peter J., Priori Silvia G., Cerrone Marina, et al. Left Cardiac Sympathetic Denervation in the Management of High-Risk Patients Affected by the Long-QT Syndrome. *Circulation* .2004;109(15):1826-1833 doi:10.1161/01.CIR.0000125523.14403.1E

11. Bos J. Martijn, Bos Katy M., Johnson Jonathan N., Moir Christopher, Ackerman Michael J. Left Cardiac Sympathetic Denervation in Long QT Syndrome. *Circ Arrhythm Electrophysiol* . 2013;6(4):705-711. doi:10.1161/CIRCEP.113.000102

12. Schwartz PJ. The Rationale and the Role of Left Slectomy for the Prevention of Malignant Arrhythmias. *Ann N Y Acad Sci* . 1984;427(1):199-221. doi:10.1111/j.1749-6632.1984.tb20785.x

13. Pj S, Ng S, Am B. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. *Am J Cardiol* . 1976;37(7):1034-1040. doi:10.1016/0002-9149(76)90420-3

14. 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;6(6):752-759. doi:10.1016/j.hrthm.2009.03.024

15. Da W, Je S, Sm T, D B. Thoracoscopy versus thoracotomy: indications and advantages. The American surgeon. Published January 1995. Accessed September 16, 2020. https://pubmed.ncbi.nlm.nih.gov/7832389/

16. Hofferberth SC, Cecchin F, Loberman D, Fynn-Thompson F. Left thoracoscopic sympathectomy for cardiac denervation in patients with life-threatening ventricular arrhythmias. *J Thorac Cardiovasc Surg* . 2014;147(1):404-411. doi:10.1016/j.jtcvs.2013.07.064

17. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* . 2013;10(12):1932-1963. doi:10.1016/j.hrthm.2013.05.014

18. Schwartz PJ, Spazzolini C, Crotti L, et al. The Jervell and Lange-Nielsen Syndrome. *Circulation* . 2006;113(6):783-790. doi:10.1161/CIRCULATIONAHA.105.592899

19. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J* . 2013;34(40):3109-3116. doi:10.1093/eurheartj/eht089

20. Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. *Heart* . Published online May 26, 2021. doi:10.1136/heartjnl-2020-318259

21. Nair AS, Nirale AM, Gopal T, Sriprakash K. A child with Jervell and Lange-Nielsen syndrome for permanent pacemaker implantation and sympathectomy: Anesthesia management and considerations. *J Anaesthesiol Clin Pharmacol* . 2015;31(4):573. doi:10.4103/0970-9185.169101

22. Eldar M, Griffin JC, Abbott JA, et al. Permanent cardiac pacing in patients with the long QT syndrome. *J Am Coll Cardiol* . 1987;10(3):600-607. doi:10.1016/S0735-1097(87)80203-6.