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Physical and Psychological Consequences of Left Cardiac Sympathetic Denervation for Long QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia

Running title: *Waddell-Smith et al.; Left cardiac sympathectomy for LQTS and CPVT*

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Abstract:

Background - Left cardiac sympathetic denervation (LCSD) reduces risk in long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Side effects and patient satisfaction have not been systematically analyzed in this population. Study aims included documenting physical and psychological side effects and patient satisfaction after LCSD for LQTS or CPVT.

Methods and Results - Patients with LQTS (40) and CPVT (7) underwent video-assisted thoracoscopic LCSD, median follow-up 29 months (range: 1-67). Clinical records were reviewed, 44 completed a telephone survey. 25/47 (53%) were symptomatic pre-operatively (syncope 15, near drowning 7, resuscitated sudden death 3). Indications: beta-blocker intolerance (15, 32%) or non-adherence (10, 21%), disease factors (18, 38%; CPVT (6), near drowning (2), exertional syncope (1), symptoms on therapy (2), LQT3 (1), QTc>520 milliseconds (ms) (6)). Others proceeded due to competitive sports participation (2), family history of sudden death (1), other (1). QTc did not change (461±60ms to 476±54ms (P=0.49)). Side effects were reported by 42 of 44 (95%). 29 (66%) reported left sided dryness, 26 (59%) a Harlequin-type (unilateral) facial flush, 24 (55%) contralateral hyperhidrosis, 17 (39%) differential hand temperatures, 5 (11%) permanent ptosis (4 (9%) transient ptosis). 5 (11%) have thermoregulation difficulties, 4 (9%) a sensation of left arm paraesthesia and 3 (7%) lost their sympathetic flight/fright response. Post-operative satisfaction: 38 (86%) were happy with procedure, 33 (75%) felt safer and 40 (91%) recommend the procedure. 40 (91%) patients were happy with their scar.

Conclusions - Despite significant morbidity resulting from LCSD, patients with LQTS and CVPT have high levels of post-operative satisfaction.

Keywords: long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, sympathectomy, side effects, video-assisted thoracoscopic

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Introduction

Video-assisted thoracoscopic (VATS) sympathectomy is used to treat various disorders, most commonly focal hyperhidrosis and facial blushing.[1] The procedure (when the lower part of the left stellate ganglion and first 4-5 thoracic ganglia are ablated) also significantly reduces the occurrence and frequency of symptoms in long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), even in very high risk populations.[2-7]

Side effects of sympathectomy have been well documented in the hyperhidrosis and blushing populations, and include compensatory/reflex hyperhidrosis, pain, gustatory sweating and Horner's syndrome.[8-10] However, there is scant acknowledgement of these symptoms in cardiology literature. In order to make a balanced decision regarding the risk-benefit ratio for this procedure, and to counsel our patients appropriately to make an informed choice, clinicians need to appreciate the experience of patients who have had the procedure previously for the same indications. This study reports the physical and psychological consequences, and impression of satisfaction among patients who have undergone video assisted thoracoscopic left cardiac sympathetic denervation (LCSD) in the management of either LQTS or CPVT. To our knowledge, it is the first study to do so.

Methods

Study population

All forty-seven patients who have undergone a minimally invasive video-assisted LCSD for the treatment of LQTS or CPVT in New Zealand were included. All were enrolled in the New Zealand Cardiac Inherited Diseases Registry and consented to their data being used for research.[11] Procedures were performed between 2008-2014 by one of two surgeons; median age at time of LCSD was 17 years (range 2-64), 34 females (72%) and 13 males. Patients who had

the same procedure for other indications, or who had open surgery, were excluded. Pre-treatment counselling was carried out by the senior author and the surgeon performing the procedure.

An experienced clinician made a clinical diagnosis of LQTS or CPVT, and genotyping has subsequently been attempted in all but one patient.[11] Referral for LCSD was made as deemed clinically appropriate.

Data collection

Patient information

Demographic and clinical data was obtained from medical records, most of which was stored prospectively as part of the registry. Clinical diagnosis, genotype, mutation, most severe symptom pre LCSD, medical therapy pre and post procedure, indication for and details about procedure were recorded. Unless otherwise specified, age is at LCSD and mean/median QTc is for LQTS patients only.

Physical and psychological consequences of LCSD

A single questionnaire was administered via telephone by the first author to subjects over 18 years of age (n=25), or their parent if younger at the time of the survey (n=18) (see Supplemental Material). One teenager responded alone with parental consent. Questions were constructed to retrospectively assess baseline level of psychosocial stress, overall satisfaction and physical and psychological sequelae from the procedure. Half of the questions provided scores out of five. In regards to feelings of anxiety or depression, adult and paediatric patients and parents were asked to rate how often they felt anxious or depressed where 1 was ‘none of the time’ and 5 was ‘all of the time’. Answers were documented, analyzed for common themes and notable side effects. Institutional ethical approval was gained prior to survey administration.

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ECG analysis

12-lead ECG analysis was performed by the first author blinded to patient identity, genotype and clinical situation. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave (defined using the "tangent technique" where the tangent of the steepest slope of the second limb of the T-wave crosses the isoelectric line).[12] Bazett's correction was used, and the longest measurement of lead II or V5 was taken from ECGs taken the day before and after LCSD, or as near to this time as possible.

Statistical analyses

Assumptions of the t-test were tested, and all data analyzed by unpaired parametric and non-parametric tests as appropriate, including 2-way ANOVA, unpaired t-test and column statistics. Statistical analyses were performed using GraphPad Prism version 6.0e for Mac, GraphPad Software, La Jolla California USA, www.graphpad.com and with SAS version 9.4, Cary, North Carolina, USA.

Surgical technique

Surgeons performed the procedures using VATS surgical approaches with double lumen endotracheal intubation and selective deflation of the left lung. Resection of the sympathetic chain was performed using minimally invasive techniques via either one or three axillary ports. The proximal extent of sympathectomy was either "aggressive" which included sacrificing the lower third to lower half of the stellate ganglion (n=13, 28%) or "conservative" which involved sparing the majority of the lower third of the stellate ganglion (n=34, 72%). The mean age was lower in the "aggressive" group compared with the "conservative" group (16.5 years versus 26 years, P=0.04). When comparing the "aggressive" and "conservative" groups there were no significant differences according to sex (with a preponderance of females in both groups, 8

(69%) versus 25 (74%), P=0.3) or underlying disease (LQTS versus CPVT, P=1.0). Intraoperative intercostal drains were not used and at the end of the procedure air was evacuated. Patients were admitted to the intensive care unit post operatively, and discharged home after a median of 1 day (range 0-13 days). One patient self-discharged on day 0, and the 13 day admission was due to complex management issues in a patient with Jervell and Lange-Neilsen syndrome, unrelated to LCSD. All other patients had 1-2 days of post-operative stay.

Results

Clinical cohort

All patients had unequivocal phenotypic evidence of disease, 40 with LQTS and 7 with CPVT.[11] Further details of the study cohort are shown in Table 1 and Figure 1.

The most common indication for LCSD related to medical therapy: 15 (32%) were unable to take beta-blockers due to intolerance or contraindication such as asthma, and a further 10 (21%) were non-adherent with therapy.

Baseline psychological status

Self-reported retrospective scores of anxiety and depression were provided by adult patients, and by parents of affected children on behalf of themselves and their child if the patient was less than 18 years old at the time of the survey.

Adult patients (>18 years)

24 of 25 adults answered the questions about pre-operative anxiety and depression; median anxiety score was 2.5 (range 1-4: i.e. anxious none to most of the time respectively) and baseline depression median score was 1 (range 1-4). Seven adults (29%) reported feelings of anxiety related to LQTS/CPVT most of the time and 6 (25%) reported feeling depressed most of the time.

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Paediatric patients

Nineteen of the 26 paediatric patients were still less than 18 years old at the time of the survey and for this cohort, parents were asked about their own and child's baseline scores. However, one child was too young (4 years old) at the time of surgery for the parents to assess psychological status, one parent was unable to answer the questions on behalf of their child and one teenager answered the questions by herself (after parental consent). Retrospectively, parents' self-reported median anxiety and depression scores were 3 (range 1-4). They rated their child's pre-operative baseline anxiety and depression with median scores of 1 (range 1-5). Five children were given a score by their parents of 4 or 5 out of 5 for anxiety and/or depression. Out of the 17 paired parent/child responses, baseline psychological scores were similar except in 5 cases where anxiety/depression was much higher in 3 parents than their children and much higher in 2 children.

Patient's depression and anxiety was highly correlated amongst the cohort (Spearman correlation 0.84).

Post-operative course

Follow-up by telephone survey and review of case notes was performed after a median of 29 months following LCSD (range 1-67 months). Table 2a shows patient comments regarding side-effects.

General recovery

Most (79%) patients were very satisfied with their operation overall when considering pain relief, side effects, physical and emotional recovery and economic considerations, see Table 3. There was no significant relationship between satisfaction and pre-operative depression or anxiety (P=0.12 and 0.08 respectively), length of post-operative follow-up (P=0.17) or severity

of pre-operative symptoms (P=0.61). Figure 2 and Table 3 show the 44 patients who completed the survey, their side effects and survey response scores.

Follow-up occurred over a median of 29 months post-operatively (range 1 month-5 years and 7 months). There was no peri operative mortality or major complications requiring surgical reintervention. One death occurred 47 months following LCSD, but this was non-cardiac and unrelated to the procedure.

Cardiac events

During 116 patient-years of follow-up, 1 patient with LQTS, 1 with Jervell and Lange-Nielsen LQTS and three with CPVT experienced cardiac events (i.e. 1+1/40 LQTS patients,5%; 3/7 CPVT patients, 43%). This did not vary with degree of sympathetic resection (LQTS P=0.45, CPVT P=0.43). The patient with single mutation LQTS was 17 years old at LCSD, carries the KCNQ1 c.797T>C missense mutation and her longest QTc pre-operatively was 522 milliseconds (ms). QTc prior to procedure was 483ms and 431ms two years following. Both pre and post operatively she has been adherent with controlled release metoprolol, and her worst symptom (in both time periods) was classic arrhythmic syncope which resulted in implantable cardioverter defibrillator insertion following the post-operative event. Five of the seven CPVT patients had their procedure performed before flecainide was known to be therapeutic.[13] Of the three patients with CPVT who experienced post-operative cardiac events; one refused medical therapy, one was on low dose beta-blockade without up-titration due to failure to attend follow-up appointments, and the third was on both nadolol and flecainide at the time of her arrest. There is no relationship between degree of sympathetic resection and occurrence of post-operative symptoms.

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Electrocardiographic changes

Pre-operatively, median QTc amongst LQTS patients was 461±60ms and post-operatively was 476±54ms (P=0.49).

Physical sequelae

Dry skin

The most common reported effect from the procedure was dry skin on the left side of the body (67%). Twenty-nine patients reported a dry left hand, including 3 who also reported a dry face (left side), and 3 with dry left foot. Seven patients volunteered using extra (or stronger) moisturiser on the left side.

Harlequin type facial flush

The second most common effect was having a marked Harlequin type demarcation in colour on, at least, the face (63%). Seventeen reported this on the face only, 3 on the hand only, 5 on the whole body, and 8 reported the phenomenon worsening after exertion (see Figure 3a).

Compensatory hyperhidrosis

Fifty-five percent reported problems with excessive right sided sweating (see Figure 3b). Lifestyle adjustments include use of heavy-duty antiperspirant (including the lumbar back), always carrying a towel, and using grip aids to play sport (with the dry left hand losing grip). One said they use grip aids due to sweaty right hand, another said they slip due to dry left hand, and a third uses sticky stuff on her hand whilst playing netball (parent unsure of side).

Pain

Five patients reported severe pain in hospital necessitating extra analgesia (11%). Three patients (7%) experienced a shooting type of pain down the left side resolving after 1-8 months. No patients have chronic pain and one patient reported resolution of her pre-existing chronic upper

back pain.

Hand temperature

Eleven patients (25%) reported significant differences in the temperature of their hands, although which hand was warm and which was cold differed between the group, and not all able to recall.

Thermoregulation difficulties

Five patients (11%) reported a definite hot and cold side of the body (50:50 for right/left). They commented that it was difficult to regulate their body temperature, particularly in bed or in cold weather.

Ptosis

Nine patients reported left sided ptosis. In four individuals, this was transient lasting between 3 days and approximately 6 months. Five patients (11%) have permanent ptosis (at median of 26 months follow up, range 9-55 months), all report as very mild and none report disappointment (see Figure 4). One patient reports the ptosis worsens when fatigued.

Sensation of paraesthesia

Two women (5%) report a sensation of "reduced feeling and tingling" in the left fingers and arm up to the elbow.

Emotional/psychological sequelae

Loss of sympathetic flight/fright response

Three women (7%) reported that they are much calmer in situations that previously would have been alarming or frightening. One also feels detached in sad or angry circumstances.

Satisfaction

The majority of patients were satisfied post-operatively, feeling positive, safer and happy to recommend the procedure to others (see Figure 2 and Table 2b for patient comments).

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Symptom duration

Three patients volunteered that their symptoms were worst in the first year (or two), and then improved.

Comparison of side effects according to degree of resection

When comparing the "aggressive" versus "conservative" resection groups, there were no significant differences between occurrence of dry skin (P=0.14), Harlequin-type facial flush (P=0.72), compensatory hyperhidrosis (P=1.0), differences in hand temperature (P=0.47), pain (P=0.32), thermoregulation difficulties (P=1.0), sensation of paraesthesia (P=0.56) or loss of sympathetic drive (P=0.55). When both transient and permanent ptosis are included there is a significant difference between "aggressive" (n=5/10) and "conservative" (n=3/31, P=0.009).

Discussion

The left cardiac sympathectomy, first described in 1971,[14] has recently re-emerged as an important therapeutic option for both LQTS and CPVT, and can now be performed thoracoscopically. The procedure is both safe [10] and efficacious. [5] For some patients it becomes first line therapy when beta blockers are contraindicated or cannot be tolerated. In our New Zealand population, poor long term adherence to therapy, a major hazard in those severely affected, [15] remains a significant problem. The fact that three of our patients who underwent LCSD for non-adherence can no longer be traced, underscores the potential value of this procedure in patients who only intermittently engage with health services. Nevertheless, this is a procedure with side effects, most of which are permanent, so accurate counselling prior to the procedure is essential.

The present study documents high rates of morbidity related to side effects, sometimes associated with significant levels of embarrassment and distress. The side effects described by

our cohort are consistent with those when the sympathectomy is done for other reasons, [2, 8-10, 16] and may be more severe due to the necessary ablation of the second thoracic ganglion which is associated with more pronounced compensatory hyperhidrosis. [10, 17] However most other indications, such as hyperhidrosis, involve bilateral sympathectomy so the harlequin effect does not tend to occur. Furthermore, patients with LQTS and CPVT tend to have underlying anxiety [18] and sometimes depression [19] related indirectly to their condition and also to the sacrifices and life style changes they must make. They often also have a traumatic personal or family history. This background, confirmed by the baseline psychological profile in this study, may explain the overall satisfaction amongst patients with LQTS and CPVT who have undergone LCSD. The sympathectomy gives them a sense of safety and a sense that they can lead a relatively normal life. Some of the patients' quotes lend support to this, particularly "I see sympathectomy as a passage back to normal life".

Prior to this investigation, we and others have tended to counsel our patients that permanent ptosis was the most significant (but uncommon) side effect.[20] However, in this study, patients often recalled their side effects with some distress. They describe embarrassment, inconvenience and annoyance. We are now able to give a more thorough and honest account of life after a LCSD. The findings of this review has resulted in a change of emphasis in our consenting practice, being careful to highlight the compensatory hyperhidrosis, Harlequin type facial flush etc., as well as the less common and very mild ptosis. Advising them of the overwhelming patient satisfaction is as important as warning of the side effects. Regarding the occurrence of Horner's syndrome, we found no difference in development of permanent ptosis according to surgical technique, but given the low prevalence, a larger series may be needed to clarify this.

This study adds a new perspective to the side effects experienced from sympathectomy. In LQTS and CPVT populations, previous reports suggest the side effects of LCSD are "mild" and "very limited". [21] In comparison, previous reports of side effects in the large cohorts where sympathectomy is performed for hyperhidrosis or facial flushing, reporting of side effects has been physician based; [8, 9] patient commentary is excluded and satisfaction may be perceived differently as the procedure was cosmetic. [10] The majority of patients in our cohort would strongly disagree that side effects are minimal, but agree that they are outweighed by the benefits. [21]

This study was not designed to examine assess efficacy of reducing cardiac events, nevertheless there are still important findings. In case reports and small series, LCSD has significantly reduced the occurrence of cardiac events in patients with CPVT. [2, 7, 22-27] In the largest and most recent series published, 54 symptomatic patients with CPVT underwent LCSD. Although the number of patients who had an incomplete LCSD was small, the authors report that those who had a complete LCSD were much less likely to suffer post-operative cardiac events compared with those who had an incomplete denervation (8/47 (17%) vs 5/7 (71%), P<0.01).[27] Six patients (86%) were symptomatic pre-operatively, and 3/7 (43%) were symptomatic post operatively (post-operative follow-up median 45 months, range 6-67months, 24 patient years). Therefore it should be emphasised that long term adherence with medical therapy, importantly containing flecainide, is paramount in the care of individuals with CPVT.

A limitation of this study is the reliance on patient reporting and lack of objective measures. This may result in a higher incidence of reported side effects when compared with other series. Non-confidential responses may introduce bias, but given the high morbidity reported, we feel the impact of this would be minimal. Furthermore, no validated questionnaire

was suitable for this study cohort. Whilst there are inherent challenges with interviewing children and there may be a discordance between parental and child responses, we performed an ordinal logistic regression excluding parental data to minimise this issue. Follow-up is variable and less than one year in 23% of the cohort, a time when side effects are more pronounced (both in our series and others).[8]

Conclusion

This study documents for the first time, side effects and patient satisfaction relating to minimally invasive video-assisted thoracoscopic left cardiac sympathetic denervation in LQTS and CPVT populations. Whilst morbidity was high (most commonly due to dry skin, compensatory hyperhidrosis and Harlequin type facial flush), so too was patient satisfaction, with 91% of patients recommending the procedure to a similarly affected person. Extent of surgical resection influenced risk of ptosis, but not other outcomes. This study enables us to better counsel patients prior to undergoing this treatment.

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References:

1. Hashmonai M, Kopelman D. History of sympathetic surgery. *Clin Auton Res*. 2003;13 Suppl 1:I6-9.

2. 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;147:404-409.

3. 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;6:752-759.

4. Bos JM, Bos KM, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation in long QT syndrome: analysis of therapeutic nonresponders. *Circ Arrhythm Electrophysiol*. 2013;6:705-711.

5. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, Bloise R, De Ferrari GM, Klersy C, Moss AJ, Zareba W, Robinson JL, Hall WJ, Brink PA, Toivonen L, Epstein AE, Li C, Hu D. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation*. 2004;109:1826-1833.

6. Li J, Liu Y, Yang F, Jiang G, Li C, Hu D, Wang J. Video-assisted thoracoscopic left cardiac sympathetic denervation: a reliable minimally invasive approach for congenital long-QT syndrome. *Ann Thorac Surg*. 2008;86:1955-1958.

7. Schneider HE, Steinmetz M, Krause U, Kriebel T, Ruschewski W, Paul T. Left cardiac sympathetic denervation for the management of life-threatening ventricular tachyarrhythmias in young patients with catecholaminergic polymorphic ventricular tachycardia and long QT syndrome. *Clin Res Cardiol*. 2013;102:33-42.

8. Bryant AS, Cerfolio RJ. Satisfaction and compensatory hyperhidrosis rates 5 years and longer after video-assisted thoracoscopic sympathotomy for hyperhidrosis. *J Thorac Cardiovasc Surg*. 2014;147:1160-1163.e1.

9. Kapetanos AT, Furlan AD, Mailis-Gagnon A. Characteristics and associated features of persistent post-sympathectomy pain. *Clin J Pain*. 2003;19:192-199.

10. de Andrade Filho LO, Kuzniec S, Wolosker N, Yazbek G, Kauffman P, Milanez de Campos JR. Technical difficulties and complications of sympathectomy in the treatment of hyperhidrosis: an analysis of 1731 cases. *Ann Vasc Surg*. 2013;27:447-453.

11. Earle N, Crawford J, Smith W, Hayes I, Shelling A, Hood M, Stiles M, Maxwell F, Heaven D, Love DR, Skinner JR. Community detection of long QT syndrome with a clinical registry: an alternative to ECG screening programs? *Heart Rhythm*. 2013;10:233-238.

12. Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm*. 2008;5:1015-1018.

13. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, Shimizu W, Sumitomo N, Fish FA, Bhuiyan ZA, Willems AR, van der Veen MJ, Watanabe H, Laborderie J, Haissaguerre M, Knollmann BC, Wilde AA. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol*. 2011;57:2244-2254.

14. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *N Engl J Med*. 1971;285:903-904.

15. Vincent GM, Schwartz PJ, Denjoy I, Swan H, Bithell C, Spazzolini C, Crotti L, Piippo K, Lupoglazoff JM, Villain E, Priori SG, Napolitano C, Zhang L. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures". *Circulation*. 2009;119:215-221.

16. Atallah J, Fynn-Thompson F, Cecchin F, DiBardino DJ, Walsh EP, Berul CI. Video-assisted thoracoscopic cardiac denervation: a potential novel therapeutic option for children with intractable ventricular arrhythmias. *Ann Thorac Surg*. 2008;86:1620-1625.

17. Alvarez MA, Ruano J, Gomez FJ, Casas E, Baamonde C, Salvatierra A, Moreno JC. Differences between objective efficacy and perceived efficacy in patients with palmar hyperhidrosis treated with either botulinum toxin or endoscopic thoracic sympathectomy. *J Eur Acad Dermatol Venereol*. 2013;27:e282-288.

18. Hamang A, Eide GE, Rokne B, Nordin K, Bjorvatn C, Oyen N. Predictors of heart-focused anxiety in patients undergoing genetic investigation and counseling of long QT syndrome or hypertrophic cardiomyopathy: a one year follow-up. *J Genet Couns*. 2012;21:72-84.

19. Hintsa T, Keltikangas-Jarvinen L, Puttonen S, Ravaja N, Toivonen L, Kontula K, Swan H. Depressive symptoms in the congenital long QT syndrome. *Ann Med*. 2009;41:516-521.

20. Schwartz PJ. Efficacy of left cardiac sympathetic denervation has an unforeseen side effect: medicolegal complications. *Heart Rhythm*. 2010;7:1330-1332.

21. Odero A, Bozzani A, De Ferrari GM, Schwartz PJ. Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias: the surgical supraclavicular approach to cervicothoracic sympathectomy. *Heart Rhythm*. 2010;7:1161-1165.

22. Wilde AA, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, Ferrandi C, Koolbergen DR, Odero A, Schwartz PJ. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med*. 2008;358:2024-2029.

23. Salvi V, Karnad DR, Panicker GK, Natekar M, Hingorani P, Kerkar V, Ramasamy A, de Vries M, Zumbrunnen T, Kothari S, Narula D. Comparison of 5 methods of QT interval measurements on electrocardiograms from a thorough QT/QTc study: effect on assay sensitivity and categorical outliers. *J Electrocardiol*. 2011;44:96-104.

24. Makanjee B, Gollob MH, Klein GJ, Krahn AD. Ten-year follow-up of cardiac sympathectomy in a young woman with catecholaminergic polymorphic ventricular tachycardia and an implantable cardioverter defibrillator. *J Cardiovasc Electrophysiol.* 2009;20:1167-1169.

25. Scott PA, Sandilands AJ, Morris GE, Morgan JM. Successful treatment of catecholaminergic polymorphic ventricular tachycardia with bilateral thoracoscopic sympathectomy. *Heart Rhythm*. 2008;5:1461-1463.

26. Gopinathannair R, Olshansky B, Iannettoni M, Mazur A. Delayed maximal response to left cardiac sympathectomy for catecholaminergic polymorphic ventricular tachycardia. *Europace*. 2010;12:1035-1039.

27. De Ferrari GM, Dusi V, Spazzolini C, Bos JM, Abrams DJ, Berul CI, Crotti L, Davis AM, Eldar M, Kharlap M, Khoury A, Krahn AD, Leenhardt A, Moir CR, Odero A, Olde Nordkamp L, Paul T, Roses INF, Shkolnikova M, Till J, Wilde AA, Ackerman MJ, Schwartz PJ. Clinical management of catecholaminergic polymorphic ventricular tachycardia: The role of left cardiac sympathetic denervation. *Circulation*. 2015;131:2185-2193.

Table 1: Baseline characteristics of the study cohort

	LQTS (n=40)			CPVT (n=7)		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
Genotype and Sex						
KCNQ1	6	17	23	-	-	-
KCNH2	3	8	11	-	-	-
SCN5A	0	1	1	-	-	-
Gene negative	3	2	5	-	-	-
RyR2	-	-	-	1	5	6
Untested	-	-	-	0	1	1
Pre-operative symptoms						
Cardiac arrest			2			1
Near drowning			6			1
Syncope			12			4
Asymptomatic			20			1
Pre-operative beta-blockade						
Nadolol			14			3
Metoprolol controlled release			9			2
Atenolol			1			0
Indications for LCSD for the entire cohort (n=47)						
Medical therapy						
Beta-blocker intolerance or contraindication			14			1
Beta-blocker non-adherence			10			0
Disease related factors						
Disease			1*			6†
Aggressive disease			3‡			0
Symptoms on medical therapy			2			0
QTc>550ms			5			0
QTc>520ms and near drowning			1			0
Patient choice						
Family history SCD			1			0
Desire to perform high level sports			2			0
For increased sense of safety			1			0
Indications for LCSD for the asymptomatic cohort (n=21)						
Medical therapy						
Beta-blocker intolerance or contraindication (%)			7			0
Beta-blocker non-adherence			5			0
Disease related factors			1*			2†
QTc≥560ms			3			
Patient choice (%)			3			

*LQT3; †CPVT; ‡3 paediatric patients presenting respectively with near drowning, syncope during running race and syncope under water
§ SCD: sudden cardiac death

Table 2a: Patient and caregiver comments describing side effects occurring after LCSD for LQTS or CPVT

Dry skin	Old lady skin on the left side. My left hand doesn't crinkle, even in the pool.
Harlequin type facial split	Jekyll and Hyde. Embarrassing.
Compensatory hyperhidrosis	It's really bizarre. I'm a freak, a smelly freak on the right hand side. Embarrassing! I'd get the other side done, but then where would all the sweat go?!
Differential hand temperatures	Ice cold left hand.
Difficulties in temperature regulation	One hot side and one cold side make it difficult in bed.
Emotional and psychological sequelae	Now I get butterflies in my stomach instead of fast heart beats and faints/seizures. I feel more detached, and don't feel embarrassed, sad, angry or disappointed anymore. Not getting angry is a bonus with a 15 year old daughter. At times I know that I'm angry, but I don't have a fright/flight response, I have no startle response, and have a dull thud feeling instead. I don't actually feel sad when I hear sad/bad news. I recognize the situation is a sad one, so cognitively adjust my behaviour and response accordingly. I don't get really anxious anymore, no more sudden adrenaline surges. I used to hate getting a fright, but now there is much less of a jolt, and I'm much calmer with frights.

Table 2b: Patient and caregiver comments describing satisfaction having had LCSD for LQTS or CPVT

I see sympathectomy as a passage back to normal life.
Peace of mind for parents. Do it the "sooner the better". Extra insurance.
Made my life better. I wish it was done earlier. Ends suffering.
Reduces risk of sudden death, its lifesaving, and the benefits far outweigh the side effects.
Might as well have it done, because no difference afterwards (back to normal). I'm safe; it's an extra thing to be safe.
Eliminates worry, and if something happens in the future, I don't have to think 'what if?'
Helps keep you alive, wouldn't want to be left wondering.
It's given me confidence; I've done something to make me safer.

Table 3: Post-operative physical and psychological consequences of LCSD, post-operative satisfaction

Post-operative physical and psychological sequelae of LCSD	**n (%)**
Dry skin	29 (67%)
Harlequin type flush	27 (63%)
Hyperhidrosis	24 (56%)
Pain	8 (19%)
Difference in hand temperature	11 (26%)
Thermoregulation difficulties	5 (12%)
Ptosis (permanent plus transient)	9 (21%)
Ptosis (permanent)	5 (12%)
Ptosis (transient)	4 (9%)
Paraesthesia	2 (5%)
Loss of sympathetic flight/fright response	3 (7%)
Post-operative satisfaction	34/43 (79%)
Feel happy with their surgical scar appearance (score 1,2 or 3 out of 5)	41/44 (93%)
Feel positive after procedure (positive versus negative)	35/41 (85%)
Feel safer after procedure (score 1 or 2 out of 5; the remainder felt the same as pre-operatively, score 3/5)	33/44 (75%)
Feel happy the procedure happened (score 1 or 2 out of 5)	38/44 (86%)
Feel no regret that the procedure happened (score 4 or 5 out of 5)	40/44 (91%)
Would recommend the procedure to someone like you/your child (yes versus no, unsure)	40/44 (91%)

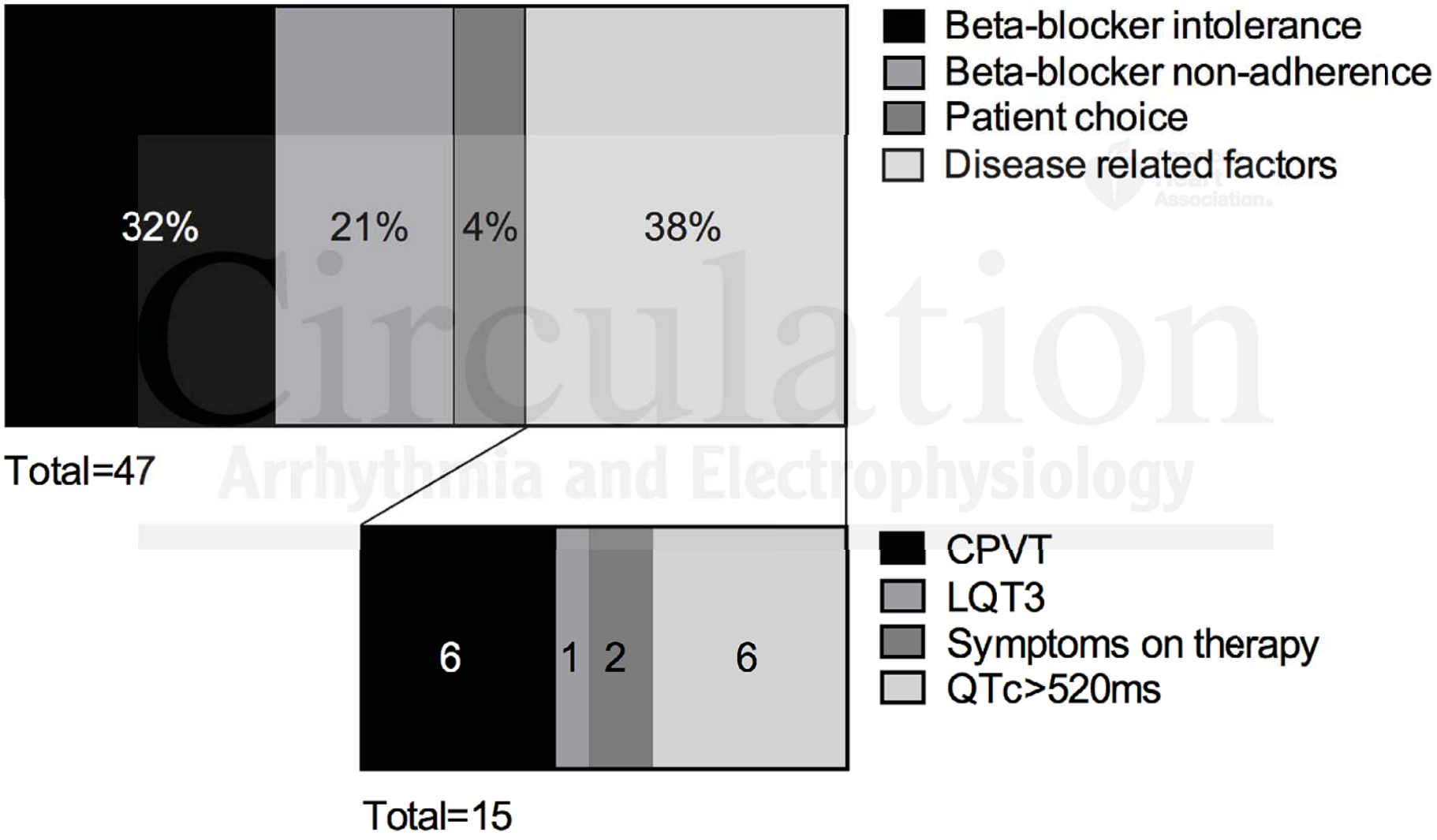
Figure Legends:

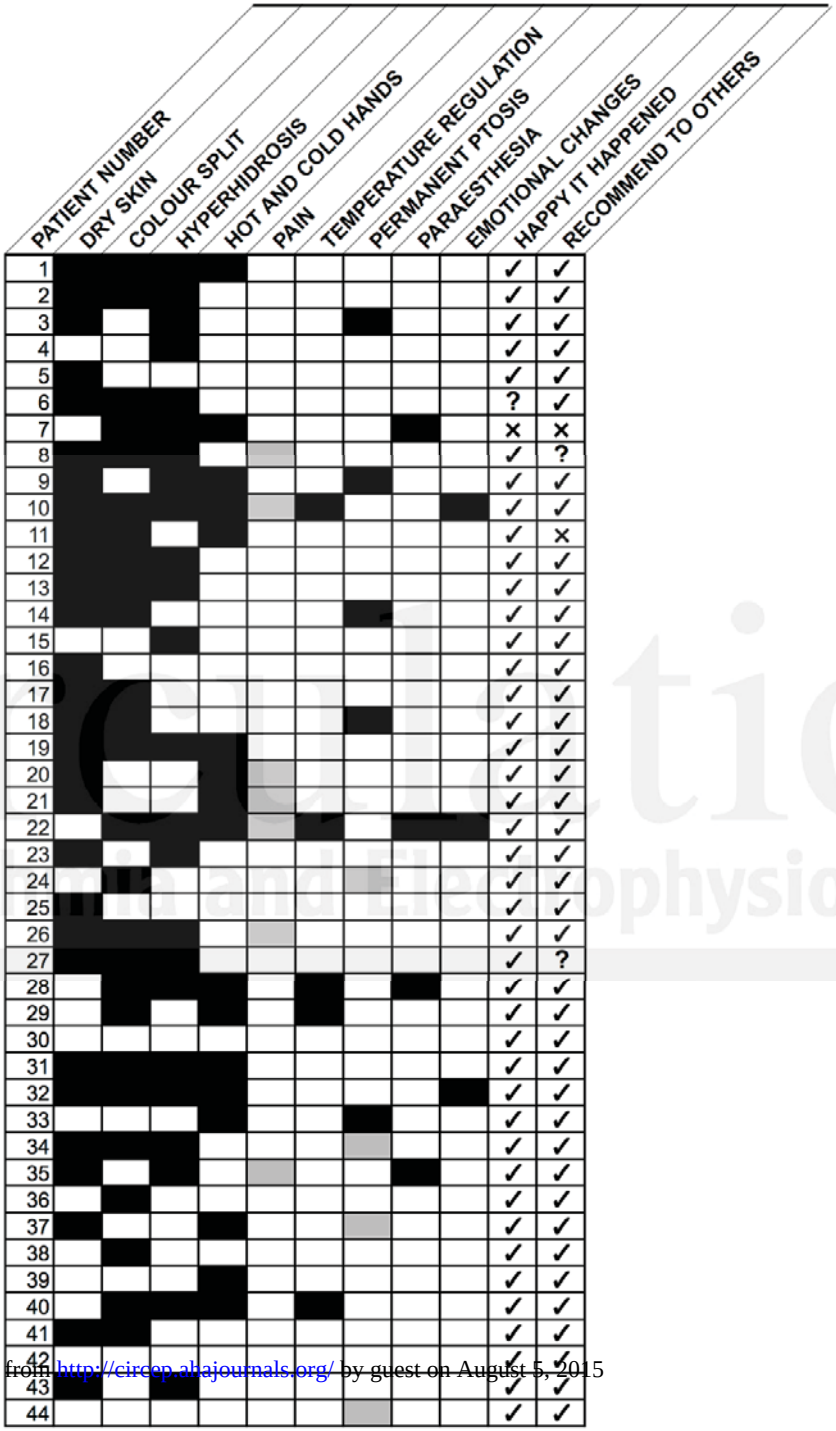
Figure 1: Major indication for each patient for LCSD included beta-blocker intolerance/contra-indication, beta-blocker non-adherence, disease related factors and patient choice. Disease related factors include those with CPVT, LQT3, those who experienced symptoms whilst compliant with medical therapy, or those with a prolonged QTc (>550ms, or >520ms with another indication). Patient choice includes those patients who had family history of sudden cardiac death, wished to perform high-level sport, or other.

Figure 2: Results from forty-four patients who completed the telephone follow-up survey. Black boxes represent symptoms, grey boxes indicates transient symptoms. Ticks represent that patients are happy the procedure happened (score 4-5 out of 5) and would recommend the procedure to a similarly affected person. Question marks represent that the patients feel neutral towards the procedure or recommending it to others. Crosses represent the patient was unhappy that the sympathectomy occurred (score 2 out of 5) or that they would not recommend the procedure to others.

Figure 3: Patient 10 following 10.1METS of exercise demonstrating (a) the Harlequin type facial flush, with flushed right side of face, and normal/pale left side and (b) the differences in sweating, with sweaty right side of face and dry left side.

Figure 4: Patient 3 has permanent left eyelid ptosis and miosis.





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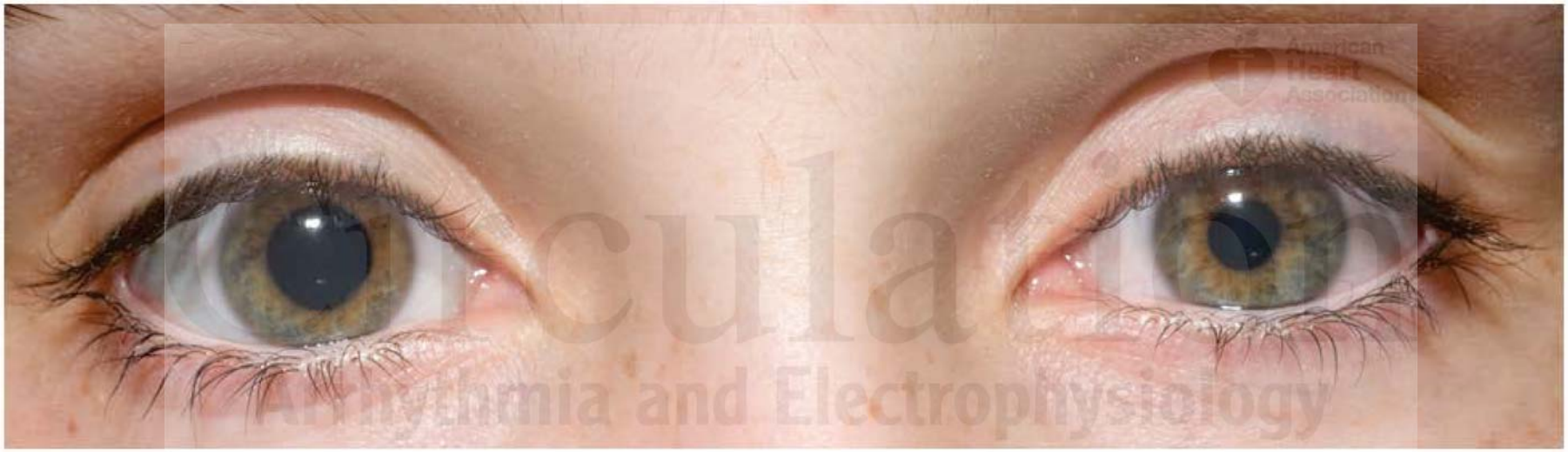

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Physical and Psychological Consequences of Left Cardiac Sympathetic Denervation for Long QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia

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