Journal of Arrhythmia 32 (2016) 340–343

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Review

Left cardiac sympathetic denervation: An important treatment option for patients with hereditary ventricular arrhythmias

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ARTICLE INFO

Article history:
Received 12 June 2015
Received in revised form
14 July 2015
Accepted 14 August 2015
Available online 29 October 2015

Keywords:
Cardiac arrhythmia
Sympathectomy

ABSTRACT

Medications such as ß-blockers are currently the primary treatment for patients with hereditary arrhythmia syndromes such as long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). However, these drugs are ineffective in some patients, and the other treatment option, that is implantable cardioverter defibrillator (ICD) implantation, is associated with significant complications in young and active patients. Left cardiac sympathetic denervation (LCSD) may reduce the wide gap between life-long ß-blocker medication and ICD implantation. Although LCSD is highly effective in prevention of cardiac events in patients with LQTS and CPVT, it is rarely used. The recently introduced procedure video-assisted thoracoscopic LCSD is associated with short hospital stays and low morbidity. Thus, LCSD is an important therapeutic option for patients with LQTS and CPVT.

Contents

1. Introduction

There are several options for the treatment of hereditary ventricular arrhythmias such as long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Administration of ß-blocker medication remains a first-line treatment; nevertheless, certain patients may be refractory or intolerant to these drugs [1–4]. Implantable cardioverter defibrillators (ICD) are often implanted in high-risk patients to prevent sudden death [1–4]. However, ICD implantation in young and active patients necessitates life-long and routine device replacement and is furthermore associated with device malfunction (including inappropriate shocks), infection, and psychological problems [2,4–6]. Although ICD shocks are generally effective for ventricular fibrillation; shocks for polymorphic ventricular tachycardia (VT), bidirectional VT, and electrical storm may not be effective in terminating these tachyarrhythmias; especially in CPVT patients [2,4–8]. Therefore, the clinical gap between ß-blocker medication and ICD implantation is wide and decisions regarding the correct course of treatment are consequently challenging.

Traditionally, the major clinical indications for left cardiac sympathetic denervation (LCSD) are ß-blocker intolerance or refractoriness, high risk of sudden death with ß-blocker treatment (despite the patient being asymptomatic), frequent ICD shocks, or

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http://dx.doi.org/10.1016/j.joa.2015.08.002

bridging to an ICD implantation in infants and small children [2,4,6,8–14]. LCSD is especially effective in patients with poor ß-blocker compliance as it has long-lasting effects [10,11]. LCSD in patients with frequent ICD shocks significantly reduces the number of shocks, thus improving quality of life [6,10,11]. Recently, LCSD via a video-assisted thoracoscopic surgery (VATS) approach has been used in patients with LQTS and CPVT, allowing for early ambulation and short hospital stays with minimal perioperative complications [6,13–17]. Despite these advantages, LCSD is rarely used as a supplementary therapy to ß-blocker administration and ICD implantation [1–4].

LCSD prevents norepinephrine release in the heart and raises the threshold for ventricular fibrillation without impairing myocardial contractility or reducing heart rate [18–20]. Large, multicenter studies have reported consistent efficacy for LCSD with regards to decreasing cardiac events in patients with LQTS and CPVT [6,9,10]. As LCSD is not a curative treatment and does not necessarily prevent sudden death, ICD implantation is recommended for at risk patients and LCSD remains underutilized, despite the proven benefits of this procedure [4–6,9,10]. Indeed, the most recently published guidelines for treating patients with primary arrhythmia syndromes recommend LCSD as a Class IIb treatment for patients with CPVT and as Classes I and IIa for patients with LQTS [21]. Indeed; lifestyle modifications, ß-blocker medication, LCSD, and ICD implantation can all be compared to a cautious driver, anti-lock braking systems, seat belts, and air bags in modern cars, where all of these options are complementary in the prevention of traffic accident-related injuries.

2. Discussion

2.1. Surgical techniques for LCSD

Left stellectomy was the first surgical technique developed for LCSD and involves ablation of the entire left stellate ganglion. However, this technique provides only limited cardiac protection and causes Horner syndrome [10]. An improved technique is left cervicothoracic sympathectomy, in which both the entire left stellate ganglion and the first four or five left thoracic ganglia are removed. While this too is associated with Horner syndrome, it does yield improved cardiac protection. The recently introduced high thoracic left sympathectomy (HTLS) technique, in which the lower half of the stellate ganglion and the first four or five left thoracic ganglia are removed, provides adequate cardiac protection and is associated with a very low incidence of Horner syndrome. Indeed, HTLS is the most commonly performed LCSD procedure in the majority of treatment centers and resection of the lower half of the left stellate ganglion is considered critical to the antifibrillatory effect of LCSD [6,10,22].

In conventional LCSD, the supraclavicular extrapleural approach is most frequently used [9]. In this approach, a small incision is made in the left subclavicular area, the anterior scalene muscle and phrenic nerve are retracted, the pleural ligament is cut, and the stellate ganglion and left sympathetic chain are isolated and severed [23]. Experienced centers have reported the duration of this procedure as 35–40 minutes [10]. However, conventional LCSD carries the same risks as those associated with open thoracotomy.

Video-assisted thoracoscopy has been used for upper thoracic sympathectomy for hyperhidrosis since the early 1990s. This minimally invasive technique has progressively evolved and been refined in recent years and the first report of video-assisted thoracoscopic surgery (VATS)-LCSD for patients with LQTS was published in 2003 [24]. In this procedure, patients are placed under general anesthesia and positioned in the right lateral decubitus position. Two or three

Fig. 1. Left cardiac sympathetic denervation performed using video-assisted thoracoscopic surgery.

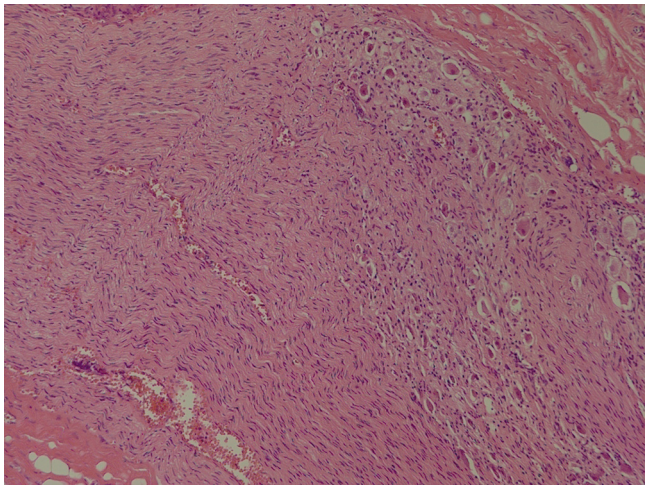

Fig. 2. A resected specimen showing wavy peripheral nerve bundles in the left field and large polygonal ganglion cells in the right field (hematoxylin–eosin stain, 40 ×).

small incisions are made in the left chest along the mid-axillary line; in order to accommodate a camera, a grasper, and an electrocautery hook dissector [15] (Figs. 1 and 2). Thoracoscopy is associated with a lower risk profile than open thoracotomy as well as reduced complication rates, shorter hospital stays, and a lower pleural drainage time [25]. Further advantages of VATS-LCSD when compared with conventional LCSD include a more extensive and accurate sympathetic chain resection due to the magnified surgical field, as well as a lower risk of Horner syndrome as less traction is applied to the stellate ganglion and sympathetic chain [12]. However, transient Horner syndrome may still develop as a result of compression and swelling of the upper half of the stellate ganglion [12,13]. When performed as described, the VATS-LCSD procedure is usually completed within an hour. While no chest tube is typically required, certain centers do routinely insert a small chest tube that is subsequently removed 1 or 2 days post-procedure. Patients are generally discharged 1 or 2 days after undergoing VATS-LCSD [12,17].

2.2. Effectiveness of LCSD

LCSD has been used to treat LQTS patients for more than 40 years. Many studies have reported the efficacy of LCSD and the

first study involving a large series of LQTS patients treated with conventional LCSD was published in 1991 [9]. After LCSD, the number of symptomatic patients decreased significantly ($p < 0.001$) from 99% to 45% and the number of cardiac events per patient decreased from 22 to 1. In 2004, the largest study investigating LCSD in LQTS patients ($n=147$) thus far was published [10]. The majority of patients were at high risk of cardiac events; 99% were symptomatic, with an extremely prolonged mean QTc interval (543 ± 65 ms); and 75% suffered from recurrent syncope after administration of maximum-dose β-blockers. After conventional LCSD, 46% of patients were asymptomatic and the mean annual number of cardiac events dropped by 91% [10]. In 5 patients who had undergone LCSD for multiple ICD shocks and electrical storms, the number of shocks experienced decreased by 95% ($p=0.02$) during the follow-up period. Interestingly, that study suggested that the results of LCSD are dependent on the experience and skill of the surgeon [10]. While a marked decrease in the number of cardiac events after conventional or VATS-LCSD is observed in the majority of studies, 20–50% of patients with LQTS remain symptomatic [9,10,12,13,15–17]. Thus, LCSD should not be viewed as a curative or alternative treatment to ICD implantation in high-risk LQTS patients [9,10,13,16], but rather as an event-attenuating procedure.

LCSD appears to be very effective in LQT1 and LQT3 patients, although certain studies with inconclusively small sample sizes have suggested it may be inadequate for the treatment of LQT8 patients [10,13,14]. Studies investigating the efficacy of LCSD for the treatment of LQTS patients with ß-blocker intolerance have shown excellent results with no cardiac events occurring during follow-up; however, the majority of patients in one study did decrease or discontinue their ß-blocker dosage [13]. This type of adjunctive LCSD treatment in ß-blocker-intolerant patients on zero or low doses of these agents appears promising. Prophylactic LCSD may also be considered for selected asymptomatic or low-risk LQTS patients as an alternative to life-long medication of uncertain significance.

The first study to investigate the effectiveness of LCSD in CPVT patients was published in 2008 [11]. Thereafter, many small studies with short follow-up periods and no definitive conclusions have been published [12,14–17,26]. A recently published multicenter study that included many of these smaller previous studies showed that LCSD was associated with a remarkable reduction in both the percentage of symptomatic patients (from 100% to 32% ($p < 0.001$)) as well as the mean annual rate of events per patient, which dropped by 92% (from 3.4 to 0.5 per person per year ($p < 0.001$)) [6]. In that study, the average number of post-LCSD ICD shocks also dropped significantly by 93% (from 3.6 to 0.6 per person per year ($p < 0.001$)) and the number of patients experiencing electrical storms was markedly reduced after LCSD (from 11 in 29 patients with ICDs (38%) to just 4 (14%)) [6]. These findings are of great significance, as the pain and fear associated with ICD shocks increases catecholamine release and could initiate electrical storms [6]. LCSD in patients with CPVT and an ICD could therefore prevent or decrease the ICD discharges associated with shock-associated sympathetic surges [6,11].

2.3. Complications of LCSD

In a previous study on conventional LCSD, Horner syndrome was observed in the majority of patients shortly after the procedure and generally ceased at a later stage [9]. Numerous recently published studies have reported no significant complications in VATS-LCSD; with the exception of a small number of cases of refractory ventricular arrhythmias, spontaneously resolving pneumothorax, and transient Horner syndrome [4,8,12–17,26]. In addition, a few cases of harlequin facial flushing and asymmetrical facial sweating, which are clinically more benign, have been reported [12,14,15,17].

There has been some concern with regards to controlling bleeding in cases of hemorrhage from the stellate ganglion artery during VATS-LCSD [22]. However, there have been no reported cases of uncontrolled bleeding or conversion to a traditional open thoracotomy during VATS-LCSD as yet.

2.4. Prediction of LCSD Efficacy

Clinical characteristics and shortened QTc intervals after LCSD are not useful for predicting the efficacy of this procedure in patients with LQTS. Average pre- and postoperative QTc values are not significantly different post-LCSD in patients with LQTS [9,10]. Normalization of QT intervals post-LCSD may occur in certain patients with LQTS, while complete suppression of syncopal episodes may be observed despite the persistence of prolonged QT intervals [9,12]. Therefore, the efficacy of LCSD should be judged only on the development of symptoms or cardiac events during the follow-up period. One multicenter study suggested that a

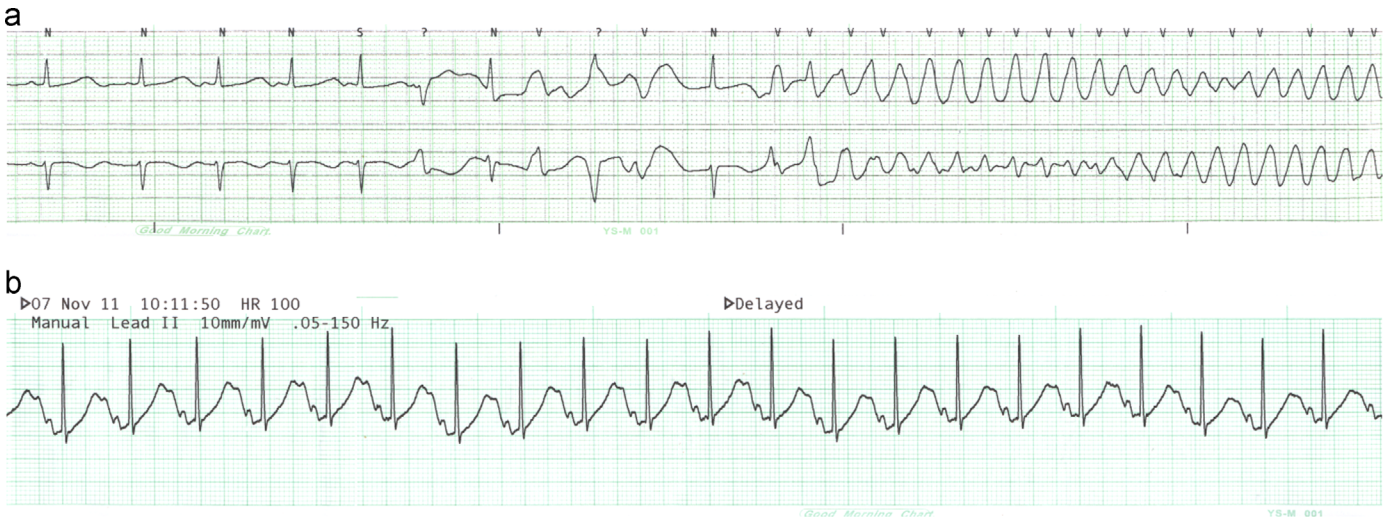

Fig. 3. Epinephrine test according to the Shimizu protocol [27] performed in a young woman with long QT syndrome and aborted cardiac arrest. The epinephrine test before LCSD (upper strip) shows a markedly prolonged QT interval and premature ventricular contraction, followed by torsades de pointes. A follow-up epinephrine test performed 5 days after LCSD (lower strip) using the same protocol shows prolonged QT intervals, but no arrhythmia. The patient remained symptom free for more than 3 years with daily ß-blocker treatment. LCSD: left cardiac sympathetic denervation.

persistently prolonged QT interval after LCSD in patients with LQTS was a significant predictor of efficacy post-procedure [10]. The results showed that patients with continued QTc ≥ 500 ms at 6 months post-LCSD remained at high risk for subsequent events; while patients with only syncope and a post-LCSD QTc < 500 ms were at a very low risk of adverse events. A further recent study showed that patients with LQTS that experienced cardiac events post-LCSD had significantly longer baseline QTcs, were more likely to have pre-procedural ICDs and, consequently, to have received pre-procedural ICD shocks when compared to patients without cardiac events post-LCSD [13]. The clinical role of the epinephrine infusion test [27] post-LCSD remains uncertain (Fig. 3).

Among CPVT patients, predictors of LCSD efficacy are unclear with the exception of extent of denervation. Patients with incomplete denervation, generally caused by sparing the lower half of the left stellate ganglion, have been found to experience significantly more cardiac events post-LCSD when compared to those with complete denervation [6].

Unfortunately, failure to treat or predict LCSD efficacy may result in sudden death in young patients. Uncertain clinical predictors and possible medicolegal conflicts could lead clinicians to recommend ICD implantation over LCSD. Thus, there is an urgent need for improved predictors before LCSD can be more widely-used, especially in moderate- to high-risk patients.

3. Conclusions

LCSD is highly effective in preventing cardiac events in patients with LQTS and CPVT and presents an important therapeutic option for these patients. Whenever syncope occurs despite optimal medical therapy, LCSD should be considered as a next step in the treatment plan.

Conflicts of interest

The author has no financial conflicts of interest to disclose concerning this review article.

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