Left Cardiac Sympathetic Denervation via Thoracoscope to Treat Long QT Syndrome

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HU ET AL.: ***Left Cardiac Sympathetic Denervation via Thoracoscope to Treat Long QT Syndrome. Purpose:*** *Long QT syndrome (LQTS) is a cardiovascular disorder characterized by prolongation of the QT interval on ECG and presence of syncope, seizures, and sudden cardiac death. The therapy for LQTS is mainly dependent on medicines. The aim of the present study was to investigate the feasibility and efficacy of a new surgical method of cardiac sympathectomy for LQTS patients.* ***Methods:*** *Left cardiac sympathetic denervation (LCSD) were conducted on 4 LQTS patients who were resistant to β-blockers. Patients' ECG and clinical symptoms were assessed before and after the surgery.* ***Results:*** *LCSD was successful in all patients. QTc decreased from 0.54±0.08 to 0.51±0.06s immediately after the procedure. However the shortened QTc returned to prior surgery level in one patient within 24 hours of the surgery. Before LCSD, horizontal bike exercise induced a significant change in T wave amplitude and prolongation in QTc. These changes diminished following LCSD. After 5-month follow-up, one patient who had frequent syncopal attacks before LCSD experienced 2 episodes of transient syncope. No syncope was reported by other patients.* ***Conclusions:*** *LCSD is a safe and effective therapy for LQTS resistant to β-blockers. These results may have significant implications in patients of developing countries like China, where expensive therapies such as implantable cardioverter defibrillator are unlikely to be widely applied due to financial constraints of the patients. (J HK Coll Cardiol 2002;10:184-190)*

Corrected QT interval, Holter monitoring ECG, horizontal bike exercise test, left cardiac sympathetic denervation, long QT syndrome(LQTS)

摘要

長 QT 綜合征(LQTS)指具有心電圖上 Q T間期延長，T 波異常，易產生室性心律失常，尤其是尖端扭轉性室速，暈厥和猝死的一組綜合征。為探討β-阻斷劑治療無效的 LQTS 經胸腔鏡行左側心交感神經切除術(LCSD)的療效，選擇4例確診為 LQTS，服用β-阻斷劑效果不佳的患者進行 LCSD。結果 4 例手術均成功，其中只有 1 例發生短暫的左眼充血和Horner's綜合征，但症狀隨後逐漸減輕，出院時幾乎完全消失。術中切除神經節後即有 QTc 縮短，平均由 0.54±0.08s 降低到 0.51±0.06s。24小時動態心電圖上測得的平均 QTc 術後與術前相比也有不同程度的縮短。臥式踏車運動試驗顯示，術前病人在運動後 T 波形態較之運動前有很大變化；而手術後再做運動試驗，運動後T 波形態較之運動前則很少發生變化；另外，術前運動引起 QTc 升高較多，而術後運動對 QTc 改變很小，提示術前 LQTS 病人受交感神經影響較大，而術後 LQTS 病人較少受交感神經的影響，說明切除交感神經的效果。術後隨訪 5 個月，4 例中有 1 例術前經常發作長時間暈厥的患者（每年7-8次以上）在術後發生過 2 次時間短暫的暈厥，初步顯示出 LCSD 手術對服用β-阻斷劑無效的 LQTS 患者有效。結論：本研究在小樣本 LQTS 病人中發現經胸腔鏡行 LCSD 手術對傳統藥物治療無效的 LQTS 病人是安全有效的。LCSD 對多數病人可縮短 QTc，預防暈厥發作，無嚴重併發症。LCSD 能否作為LQTS 的一線治療尚需進一步研究。

關鍵詞：校正的 QT 間期　24小時動態心電圖　　臥式踏車運動試驗　　左側心交感神經切除術(LCSD)　長 QT 綜合征

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Received April 30, 2002; revision accepted June 11, 2002

Introduction

The long QT syndrome (LQTS) is a cardiovascular disorder characterized by prolongation of the QT interval on ECG and presence of syncope, seizures, and sudden cardiac death.[1] According to the latest epidemiological data, the incidence for LQTS is around 1 of 5000-7000[2] and the mortality in untreated symptomatic patients is about 70%.[1,3] The young age of most patients and the high mortality in untreated symptomatic patients stress the importance of development of effective therapies.

LQTS is a genetic disease with 5 genes being identified to be responsible for its occurrence.[4] The major mode of treatment is still medications in most patients. β-blockers have been proven effective in preventing syncope in 75-80% of LQTS patients,[3,5] but more than 20% of patients continue to have syncopal episodes and remain at high risk for sudden cardiac death despite full-dose β-blockers. Experimental and clinical studies have suggested that left cardiac sympathetic denervation (LCSD) may be useful for preventing cardiac events associated with LQTS.[3] However, despite its relative simplicity, LCSD is still not widely performed in many high-risk patients partially because the physicians, or the thoracic surgeons in their hospitals, are not familiar with the procedure. The consequence is that too often, the choice goes to what appears to be the easiest approach, such as a pacemaker or an implantable cardioverter defibrillator, even when this choice may not be the best choice for many patients.[1] The present work summarized the immediate and follow up results of LCSD via thoracoscopy in 4 Chinese patients who were resistant to β-blockers.

Methods

Patient Selection

We currently have a total of 93 LQTS patients from 38 families under our care for more than 2 years. Among these patients 4 were selected for LCSD due to frequent syncope refractory to large dose of β-blockers. Patients' clinical presentation is listed in Table 1.

Surgical Procedures

Under single-lumen tracheal incubation anaesthesia, multiple port approach was used to enter the pleural cavity.[6] The sympathetic chain was identified under the parietal pleura, running vertically over the necks of the ribs in the upper costovertebral region. The left sympathetic chain between T2 and T5 was isolated and then clamped in one patient by titanium clamps (Auto Suture Company, USA) to block the sympathetic nervous truck. In other three patients the sympathetic chain was cut after clamping. In these patients the lower

Table 1. Patients' clinical history before surgery

	Case 1	Case 2	Case 3	Case 4
Sex	F	F	F	M
Age at surgery	42	36	44	6
Age at first syncope (yr)	32	7	25	0.5
Syncope	+	+	+	+
Cardiac arrest	–	–	–	–
Pharmacological therapy				
β-blockers	+	+	+	+
β-blockers+others	+	+	+	+
Cardiac events				
Rate (events/yr)	7-8	2-3	1-3	5-6
ECG parameters				
Heart rate (beats/min)	50	52	56	60
QTc(s)	0.50	0.48	0.63	0.61

+: yes; –: no

part of the left stellate ganglion was carefully removed. Care was taken to resect all the anterior branches coming off the lower part of the ganglion.

Non-invasive Tests

24 hour Holter monitoring electrocardiogram (MS8000, Marqutte Company, USA) was conducted 2 days before surgery and second day after surgery. The horizontal bike exercise test was conducted using ergometer (EGM-II, jointly made by Yueyang Instrument and Meter Plant of Hunan Province and First Hospital of Peking University, China) 2 days before and 7 days after surgery.

Measurement of QT Intervals

A 12-lead ECG was obtained before general anaesthesia. ECG was also recorded immediately before and after LCSD. Three limb lead ECGs were continuously monitored during the procedure.

QT interval of the body surface ECG was always measured on lead in which the end of T wave was clear, in most cases, on lead II or V5, sometimes on V2-V3. The corrected QT interval (QTc) was calculated according to the formula of Bazett ($QTc = QT/RR^{1/2}$), and reported in seconds. The RR interval was measured during sinus rhythm, taken the mean for at least 5 beats.

Statistical Analysis

Data were expressed as means±SD. Because patient numbers were small, no statistical analysis was attempted.

Results

LCSD was successful in all patients. There was no mortality or serious complications. After the operation, one patient developed mild Horner's syndrome, which fully resolved in 7 days without any specific intervention.

Alterations in QTc During the Surgery

The heart rate in the 4 patients remained unchanged during or after the surgery. QTc was shortened following the LCSD (Table 2).

The 6-year-old male patient experienced an episode of ventricular tachycardia (TdP) and frequent ventricular ectopics during the isolation of the sympathetic chain. However, these arrhythmias were terminated spontaneously (Figure 1).

QTc and Arrhythmias After the Surgery

The 24 hour Holter monitoring electrocardiogram

Table 2. The QTc alteration during surgery

Case	Before removal of ganglion	5 min after removal of ganglion	ΔQTc
1	0.50	0.48	0.02
2	0.46	0.46	0
3	0.55	0.52	0.03
4	0.64	0.59	0.05

Figure 1. *An episode of TdP during surgery on patient 4, a 6-year-old boy.*

showed that the mean value of QTc within 24 hours was decreased in 3 patients to various degrees, except that the QTc increased in one patient (Table 3). Among the 4 patients, there was one patient (case 1) who had frequent ventricular ectopics before surgery. After LCSD the ventricular ectopics was decreased from 1,959 to 107 beats/24 hr, and bigeminy decreased from 1,356/24 hr to 0.

Table 3. The mean QTc comparison measured by 24 hour Holter ECG

Case	1	2	3	4
Before surgery	0.46	0.48	0.53	0.61
After surgery	0.45	0.45	0.49	0.64
QTc alteration	0.01	0.03	0.04	-0.03

Exercise Tests

The horizontal bike exercise was completed in two patients. A 36-year-old female patient was house bound for 6 years due to extreme anxiety caused by syncopal attacks. She declined the exercise test before the surgery. An after-surgery exercise test was conducted but the protocol was not completed due to her poor coordination. Bike exercise test was not attempted in the 6-year-old male patient.

In the two patients who completed the exercise test, there was a significant change in the T wave morphology immediately after the test, and these changes were abolished by LCSD (Figure 2).

Before LCSD, exercise induced a greater increase in QTc. However, there was little exercise-induced increase in QTc after LCSD (Table 4).

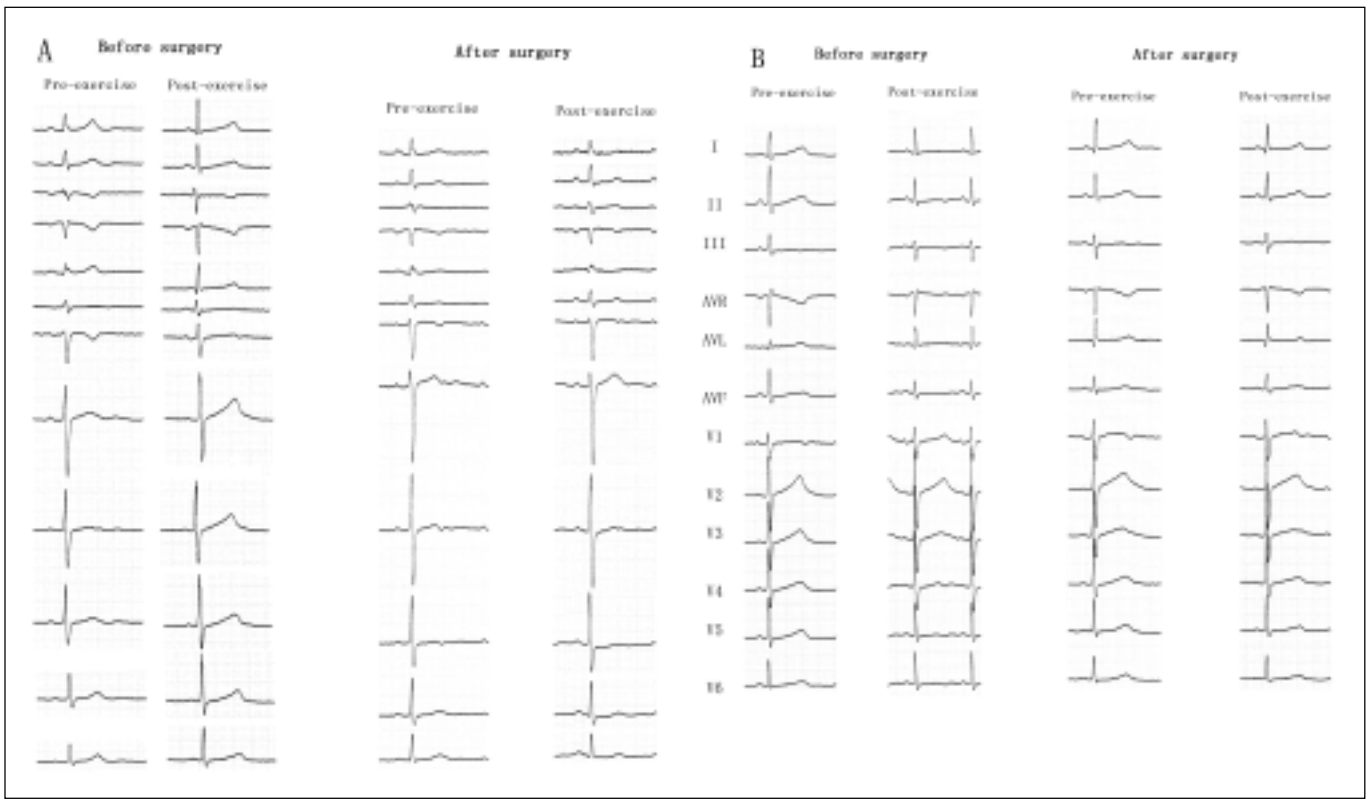

Figure 2. *The alteration of 12 lead ECG during horizontal bike exercise test before and after surgery. (A) shows that in case 1 exercise resulted in more T wave morphology change before surgery, the amplitude of T wave increased almost on all leads and that after surgery the exercise nearly resulted in no change of T wave morphology. (B) shows that in case 3 exercise resulted in more T wave morphology change before surgery, and it is manifested decrease of the amplitude of T wave and step-up of heart rate. After surgery the amplitude of T wave and heart rate were less influenced by exercise.*

Table 4. Pre- and post-exercise QTc comparison before and after surgery

	Case 1 (s)			Case 2 (s)		
	Pre	Post	ΔQTc	Pre	Post	ΔQTc
Before surgery	0.48	0.54	0.06	0.62	0.67	0.05
After surgery	0.45	0.46	0.01	0.63	0.64	0.01

Pre: data from pre-exercise; Post: data at 8 min after exercise termination; The data during exercise were not counted due to the indefinability of T wave measurement during exercise because of noises.

Follow-up

The 4 patients were followed-up for 5 months. Three patients remained symptom free. One patient who had frequent (7-8 times/yr) syncopal attacks experienced 2 episodes of brief syncope 3 months after the surgery.

Discussion

This study is the first systematic assessment of the role of LCSD in LQTS management in China. It shows that LCSD is able to shorten QTc and reduce syncopal attacks in most patients who have failed full-dose β-blocker therapy.

Rationale of LCSD for LQTS

Although the cause of long QT syndrome remains unclear, abnormal cardiac sympathetic innervation and myocardial repolarisation are believed to be responsible.[7-9] T wave alternans, one of the characteristics of long QT syndrome, can be reproduced by stimulation of the left stellate ganglion in animals[10] and in humans.[11] Animal experiments found that left stellectomy increases ventricular fibrillation threshold whereas right stellectomy decreases it.[12,13] In humans, left sympathectomy normalizes the prolonged QT interval, thereby reducing the probability of malignant arrhythmia.[3]

In 1991, Schwartz et al.[3] summarized the results of 85 LQTS patients who underwent LCSD. These patients, whose mean age at the time of surgery was 20 years, were followed for an average of 5.9 years. LCSD significantly reduced the number of patients with cardiac events, from 99% to 45% after the surgery.[3] It also diminished the number of cardiac events from 22 to 1 per patient, and shortened QTc by an average of 41 ms.[3] The 5-year survival rate in these patients was 94%.[3]

The results of our 4 patients who successfully underwent LCSD are consistent with the report by Schwartz.[3] The non-invasive tools, such as 24 hour Holter monitoring ECG and horizontal bike exercise test used before and after surgery are very useful in assessing the effect of LCSD. Continuous monitoring of a 3-lead ECG during surgery showed that following the removal or clamping of stellate ganglion and thoracic ganglia, QTc was decreased immediately in most patients. The QTc measured from Holter monitoring ECG was also decreased after surgery in most patients, indicating that this is a useful tool to assess the effect of LCSD. The analysis of ECG during exercise test demonstrated that LCSD attenuated the exercise-induced changes in T wave morphology, indicating cardiac sympathetic denervation.[14]

Techniques of LCSD

Left stellectomy involves ablation of the left stellate ganglion and often produces Horner's syndrome.[1] It provides only limited cardiac denervation in humans.[1,3] Left cervicothoracic sympathectomy involves total left stellectomy and removal of the first 4 or 5 thoracic ganglia. This procedure produces an adequate cardiac sympathetic denervation but with an associated Horner's syndrome, resulting from interruption of the nerve fibers directed to the ocular region that cross the upper portion of the stellate ganglion.[1] High thoracic left sympathectomy (HTLS) involves removal of the lower part of the left stellate ganglion and the first 4 or 5 thoracic ganglia. This procedure produces an adequate cardiac sympathetic denervation and extremely low incidence of Horner's syndrome because the ocular fibers are spared.[1,3] For these reasons, HTLS was used in our study for the surgical cardiac sympathetic denervation. There

is one patient in whom sympathetic nerve was clamped only using titanium clamps without cutting sympathetic nervous truck in our study. According to the QTc alteration measured during surgery and during exercise test before and after surgery there was no difference between the effects of clamping and cutting. Of course, there is a need to accumulate more data to draw the final conclusion.

In the earlier report by Schwartz et al[3] where left stellectomy or left cervicothoracic sympathectomy was used, there were two patients experienced chronic hyperemia of left eye, which responded to topical vasoconstrictor therapy. Horner's syndrome was present in most patients early after surgery, but almost always decreased or disappeared after surgery. In the present study where LCSD was used, there was one patient developed Horner's syndrome, which resolved after a week. These results indicate that complications like Horner's syndrome can be largely avoided via the thoracoscopic technique.

Effects of LCSD

Although LCSD may largely reduce the sympathetic innervation to the heart, it is unlikely to completely abolish the influence of catecholamines to the heart because the circulating adrenaline or noradrenaline is not affected to a significant extent by the procedure. Therefore the pathophysiology of myocyte membrane ionic channels responsible for LQTS may not be corrected completely through LCSD. As a result, QTc is decreased, but may not return to the normal level after LCSD. Therefore patients who underwent successful LCSD are still advised to take β-blockers for a period of time after surgery.

The study by Conrath et al[15] demonstrated that gender differences exist in response to β-adrenoceptor blockade in patients with types 1 and 2 of LQTS. During treatment males with LQT1 have shorter QTc interval than females and adult patients with LQT2. Also treated females with LQT1 exhibited less dispersion than those with LQT2. In our study, the gender difference of QTc shortening in response to LCSD was not seen due to the small number of patients and lack of genotyping data (genotyping work is in progress in our lab).

All our patients had frequent syncopal attacks refractory to β-blockers. During a 5-month follow-up, only one patient had a minor recurrence of symptoms whereas other patients remained symptom free. These results indicate that LCSD is effective in refractory patients in the short and media term.

Summary

This study in a small number of patients has found that LCSD via thoracoscope is a safe and effective method for the management of LQTS patients refractory to conventional pharmacological therapy. LCSD reduces QTc and prevents syncopal attacks in most patients with no serious complications. Whether LCSD can be used as a first choice of therapy in LQTS patients remains to be seen.

Acknowledgement

This study was supported by Grant 30170381 from the National Natural Science Foundation of China and grant 20011001063 of Special Foundation for Selected Doctoral Unit from the Ministry of Education of China.

Special thanks to Professor Hu Yang from the First Hospital of Peking University for his help in doing horizontal bike exercise tests.

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