

Left cardiac sympathectomy to manage beta-blocker resistant LQT patients

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Introduction

Congenital long QT syndrome (LQTS) is a disorder of prolonged cardiac repolarization, manifested by a prolonged QT interval on body surface ECG and characterized by recurrent presyncope/syncope, polymorphic ventricular tachycardia, or sudden cardiac death (1-3). This hereditary disorder is mainly caused by mutations in genes located on chromosomes 3, 4, 7, 11, 12, 17 and 21 that are responsible for the synthesis and function of potassium, sodium and calcium channels on cardiac myocytes. Molecular genetic studies have revealed a total of eight forms of congenital LQTS (2, 3). Genotype-phenotype correlation in clinical and experimental studies have been investigated in detail in the LQT1, LQT2 and LQT3 syndromes which constitute more than 90% of genotyped patients with LQTS (4, 5). These studies have enabled us to stratify risk of sudden cardiac death and to effectively treat genotyped patients.

The current therapeutic options for LQTS include anti-adrenergic therapy, implantable cardioverter-defibrillators (ICD) and permanent pacing (2, 3). Anti-adrenergic therapy with oral beta-blockers has been the mainstay of treatment, which reduces the frequency of cardiac events and sudden cardiac death in up to 70% of the patients (6, 7). However, approximately one third of the patients on beta-blockers still experience syncopal attacks and more than 10% still have cardiac arrest or sudden cardiac death during the course of therapy (6, 7).

For patients who are resistant to a full dose of beta-blockers, left cardiac sympathetic denervation (LCSD) may be used as an alternative. LCSD is associated with a high success rate in preventing cardiac events and significant reduction in mortality in LQTS patients (8-11). Surgical techniques for LCSD have been substantially improved in the last three decades. Recent advent of video-assisted thoracoscopic sympathectomy has significantly reduced the complexity of LCSD and

shortened hospital stay after the surgery (10). However, large scale clinical trials are required to evaluate the long-term effect of LCSD on sudden death in patients with congenital LQTS.

Pathogenesis of ventricular arrhythmias in LQTS

The main clinical symptoms of LQTS, presyncope and syncope, are largely due to polymorphic ventricular tachycardia (Torsade de Pointes, TdP) or ventricular fibrillation. It is believed that malfunction of potassium, sodium or calcium channels in ventricular cell membrane causes inhomogeneous prolongation in ventricular repolarization and increases in repolarization dispersion (12). The increased repolarization dispersion is responsible for the formation of circus movement or re-entry, the most common mechanism of TdP in LQTS (13). LQTS also leads to early afterdepolarization which triggers ectopic ventricular beats and initiates TdP in a heart with inhomogeneous repolarization (13).

Sympathetic activities play a crucial role in the development of arrhythmias and syncopal attacks in LQTS patients. Presyncopal or syncopal attacks are often triggered by sympathetic activation, such as startle, fright or physical exercise (2-3). Furthermore, anti-adrenergic therapy with beta-blockers reduces prevents cardiac events including TdP, further highlighting the importance of sympathetic innervation (6, 7).

LCSD in treating β -blocker resistant LQTS

β -blockers have been the mainstay of therapy for congenital LQTS for more than two decades, preventing or diminishing the risk of ventricular arrhythmia and syncopal attacks. In a study on 869 LQTS patients treated with β -blockers, the rates of cardiac events in probands and in affected family members were more than halved during a 5-year study period (6). However, 32% of patients continued to have at least one cardiac event within 5 years while on prescribed β -blockers, and 14% had another arrest (aborted or fatal) within 5 years on β -blockers (6). Obviously there is a need to explore alternative anti-adrenergic therapies in these patients who have failed on β -blockers.

Surgical removal of cardiac sympathetic innervation in LQTS patients interrupts the trigger of TdP or ventricular fibrillation and change the substrate of arrhythmogenesis in LQTS (3, 4). Earlier animal studies have found that left stellectomy increases ventricular fibrillation threshold and prolongs effective refractory periods (14, 15). In humans, left sympathectomy normalizes the prolonged QT interval, reduces QT dispersion and thereby diminishes the probability of malignant arrhythmia (8). LCSD is found to reduce the release of norepinephrine at the ventricular level and diminish the risk of early afterdepolarizations and of re-entrant mechanisms of TdP (3, 4).

Surgical techniques of LCSD

The earliest technique, left stellectomy, involves ablation of the left stellate ganglion. It often produces Horner's syndrome due to the interruption of the nerve fibers directed to the ocular region via the upper portion of the stellate ganglion (8, 9, 16). Left stellectomy provides only limited cardiac denervation in humans and does not offer adequate prevention of cardiac events (11, 16). An improved procedure, the left cervicothoracic sympathectomy, involves total left stellectomy and the removal of the first 4 or 5 left thoracic ganglia. This procedure leads to an adequate cardiac sympathetic denervation but is also associated with Horner's syndrome (8, 9, 16).

A recent advent of cardiac sympathectomy surgery is high thoracic left sympathectomy (HTLS). With HTLS, the lower part of the left stellate ganglion and the first 4 or 5 left thoracic ganglia are removed (9, 11). This procedure produces an adequate cardiac sympathetic denervation and very low incidence of Horner's syndrome, because the ocular sympathetic fibers are spared (9). For these reasons, HTLS has become a popular option for LCSD.

The major disadvantage of the above techniques is that the operation can be extensive, and patients are usually hospitalized for a number of days after the surgery. Recently, a video-assisted thoracoscopic sympathectomy has been developed to treat drug-resistant LQTS treatment (10). Under general anaesthesia, pleural cavity was entered via two small incisions in the left 3rd and 5th intercostal space at the midaxillary line. The left thoracic sympathetic chain was identified and resected from T1-T5. The lower one third of the left stellate ganglion was also removed. This procedure only requires approximately 15 min to complete and is associated with no major complications (10). Patients can be discharged 2-3 days after the surgery (10).

Effects of LCSD in the management of LQTS

To day, there has been no randomized, controlled clinical trial to systematically evaluate the long-term therapeutic effect of LCSD on LQTS. Our current knowledge on LCSD is mainly based on smaller clinical observations from various cardiology groups around the world (9-11).

The effect of LCSD on QT interval or QTc varies from patient to patient. About one third of patients will experience no significant QTc reduction after the surgery. In others, there is only a slight reduction in QTc but the clinical symptoms can be markedly improved (10, 17). However, for those who have QTc shortening, the average QTc decrease is between 30-40 ms (11, 17). Patients who continue to have a QTc of 500 ms or more 6 months after surgery are at a higher risk for subsequent cardiac events, and an ICD implant should be considered (11).

A recent review on 147 patients who underwent LCSD shows that LCSD significantly reduced serious cardiac events, such as syncopal attacks and cardiac arrest (11). After LCSD, the 5-year risk for aborted cardiac arrest and sudden cardiac death is 8% and 3%, respectively. The 5-year survival is approximately 97% (11). These results suggest that LCSD improves the clinical outcomes in patients who have not responded to a full dose of β -blockers.

It is of some interest to note that the heart rate, left ventricular function and exercise tolerance remained largely unchanged after LCSD (17). This may be due to the fact that although the cardiac sympathetic innervation is interrupted by the surgery, the systematic production catecholamines are still unaffected, which maintains the normal cardiac function and heart rate.

LCSD and ICDs

The use of ICDs in LQTS has increased substantially in recent years. ICDs are able to effectively terminate TdP or ventricular fibrillation and to prevent sudden death (2, 3) in patients with LQTS. However, it is important to realize that ICDs do not prevent the occurrence of life-threatening ventricular arrhythmias. In addition, ICDs are relatively expensive in many developing countries and their uses in LQTS patients are uncommon at this stage (7). Many patients on ICD still require anti-adrenergic therapy, such as β -blockers, to suppress arrhythmia and to reduce the number of shocks from ICD (2, 3). Recent data show that in patients who received ICD, LCSD reduces the median number of shocks by up to 95% (11). Therefore, LCSD and ICD may be used to complement each other by providing prevention of sudden death, prolonging the life span of ICD devices and improving quality of life through reduction in the number of shocks from ICDs (11).

Conclusions

LCSD is an effective anti-adrenergic therapy for drug-resistant congenital LQTS. LCSD significantly reduces the frequency of both syncope and cardiac arrest, improving 5-year survival in patients who have failed β -blocker therapy alone. Video-assisted thoracoscopic sympathectomy has simplified the LCSD procedure and may improve the acceptance of patients and their

physicians. ICSD appears to be particularly advantages in countries where ICDs are unavailable or unaffordable. ICDs remain the most effective means in preventing sudden cardiac death in patients with LQTS. When used in combination with LCSD, ICD further improves both survival and quality of life in drug-resistant patients.

References

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