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Bilateral cardiac sympathetic denervation: why, who and when?

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Cardiac electrophysiology is regulated by the autonomic nervous system (ANS) [1]. The ANS receives continuous input from the heart, integrates them, and effector signals are delivered to the heart to maintain or alter cardiac function. The initiation and maintenance of arrhythmias have been tightly linked to actions and perturbation of ANS function [2]. In particular, increased sympathetic tone is associated with arrhythmogenesis, while increased parasympathetic tone is felt to be protective. As such, extensive investigation has been dedicated to the anatomic, physiologic and biochemical factors involved in the regulation of cardiac function by the sympathetic (SNS) and parasympathetic nervous systems.

Modulation of various elements within the cardiac neural axis has been used to treat ventricular arrhythmias. These have included pharmacologic antagonism of adrenergic receptors, injection of pharmacologic agents into the stellate ganglion or thoracic epidural space, electrical stimulation of the vagus nerve or spinal cord elements via implantable devices, and surgical cardiac sympathetic denervation. Traditionally, left cardiac sympathetic denervation (LCSD) has been performed. However, bilateral cardiac

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sympathetic denervation (BCSD) may provide additional benefit in decreasing SNS output to the heart.

This article is concerned with the application of BCSD in treating ventricular arrhythmias. A focused discussion of the cardiac neural axial anatomy, and selected discussions regarding the rationale, timing, patient selection, surgical approach, outcomes and limitations of BCSD will be highlighted in this article. Parasympathetic nervous system anatomy, vagal regulation of cardiac excitability and strategies to increase vagal tone will not be addressed in this article.

Anatomy of the efferent cardiac sympathetic neuraxis

Efferent sympathetic preganglionic neurons that control cardiac function reside within the intermediate zone of the thoracic spinal cord [3]. Axons from these neurons exit via the ventral rami of segments T1–T4, to the sympathetic chain (SC). The SC lies on either side of the vertebrae and consist of paravertebral ganglia and interconnecting nerves extending from the cervical to the lumbar levels. Within the SC, preganglionic axons synapse on neurons within the stellate ganglion (fusion of inferior cervical and T1 ganglia) and ganglia at spinal levels T2–T4. The neurotransmitter released at synaptic terminals within paravertebral ganglia is acetylcholine. The left and right stellate ganglia (LSG and RSG) are the predominant ganglia from which post-ganglionic fibers to the heart arise. They exit the ganglia via gray rami communicantes and enter the left and right cardiac (cardiopulmonary) nerves, which ramify *en route* to the heart [4]. Some nerve branches are joined by parasympathetic fibers coursing to the heart [5]. Sympathetic nerve fibers arrive at the base of the heart, and penetrate the myocardium giving off smaller branches that innervate the entire heart and intrinsic cardiac ganglia as they extend to the cardiac apex. This extensive neural network tightly regulates all aspects of cardiac function on a beat-to-beat basis.

Cardiac sympathetic innervation & arrhythmogenesis

Electrophysiologic effects of LSG & RSG modulation

The regulation of cardiac function by the SNS has been recognized for nearly a century; however, adrenergic receptor antagonism is often limited by hypotension, side effects or poor adherence. In 1916, LCSD was successfully used to treat a patient with refractory angina [6]. Stellate ganglia stimulation experiments showed that LSG stimulation elicits more ventricular ectopy, caused more dispersion of repolarization across the heart, and increased the QT interval more than RSG [7]. Resection of the LSG increased the threshold for ventricular fibrillation and decreased the dispersion of repolarization, but either no effect or a decrease in threshold was observed for RSG. These observations provided the rationale for performing LCSD in patients with long-QT syndromes, as the QT interval and arrhythmia burden decreased after LCSD. Animal and human studies of postmyocardial infarction arrhythmias provided further support, as the incidence of ventricular tachycardia (VT) or ventricular fibrillation was decreased in humans and canines after LCSD.

The effects of right cardiac sympathetic denervation (RCSD) were not uniformly neutral or negative. Stimulation or resection of the RSG accelerated or slowed arrhythmias originating from the right border of an anterior infarct [8], and RSG resection in a canine model of ischemia and ventricular arrhythmias was as potent as LSG resection reducing the incidence of ventricular arrhythmias [9]. These two studies suggest an important role for RSG activity in modulating or initiating ventricular arrhythmias.

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Limitations of LCSD

A variety of reasons may account for inefficacious LCSD. Due to anatomic variability in the course of preganglionic sympathetic fibers, resection of the lower half of the stellate ganglion, as well as the ganglia of T2–T4, may not sever all sympathetic connections to the heart. Preganglionic sympathetic fibers may extend to C7 and T5 ganglia, and may assume the role previously played by the resected ganglia. Even if LCSD were initially effective, the right cardiac SC may hypertrophy and extend nerve sprouts to regions subtended by the resected left-sided ganglia, as demonstrated after unilateral superior cervical ganglion resection. LSG and RSG modulation may target specific areas of the heart (or infarct [9]), suggesting that LCSD for arrhythmias originating from a region controlled by the right-sided sympathetic nerves is likely to be ineffective.

Finally, animal studies have shown that myocardial infarction is associated with remodeling of bilateral stellate ganglia [10,11]. This process includes neuronal hypertrophy, nerve sprouting and increased synaptic vesicle density. Although the functional consequences of such remodeling remain unclear, resection of remodeled LSG alone may be insufficient, as the process of remodeling may continue in the RSG and induce the recurrence of arrhythmias.

Role of RCSD in addition to LCSD

Clinical reports of BCSD to treat severe ventricular arrhythmias date back to 1961, when successfully utilized by Estes and Izlar [12]. Since then, additional case reports or series have demonstrated the role of BCSD [13–18]. Combining these reports, 14 out of 20 patients showed a significant response to BCSD, while six patients derived no benefit. In the study published by our group, three of the six patients had undergone previous LCSD but developed arrhythmia recurrence. RCSD after prior LCSD was effective in suppressing these arrhythmias [19].

Approach to patient selection

At our center, BCSD is reserved for patients with recalcitrant arrhythmias, despite the use of pharmacologic and catheter-based therapies. For patients presenting in VT/ventricular fibrillation storm, β -blockers and other antiarrhythmics not contraindicated are used in an additive fashion. The sympathetic tone is reduced by intubation and sedation and thoracic epidural anesthesia, if needed. An interventional strategy (VT ablation) is performed and includes both endocardial and epicardial approaches. If these measures fail, the patient is referred for cardiac transplant evaluation. If the patient is felt to be a poor candidate for transplantation, cardiac sympathetic denervation is recommended. If the arrhythmia is monomorphic VT originating from the left ventricle, or if only the left ventricle is scarred, LCSD is favored, with subsequent RCSD if there is arrhythmia recurrence. BCSD is favored *a priori* if the monomorphic VT originated from a right ventricular scar (arrhythmogenic right ventricular cardiomyopathy; sarcoid), a structurally normal heart, nonischemic cardiomyopathy without scar, or if the VT is polymorphic. At our center, cardiac sympathetic denervation (CSD) is being offered up front as an adjunct to antiarrhythmics and catheter ablation of VT, even if the patient does not suffer from electrical storm, to improve upfront benefit and minimize adverse myocardial remodeling.

The video-assisted thoracoscopic or supraclavicular approach is generally favored over the open approach. The videoscopic approach may offer improved access to the lower aspects of the thoracic SC and is the initial surgical approach undertaken at our center. This approach relies on single ventilation of the contra-lateral lung while the ipsilateral thoracic SC is being resected. In an analysis of over 2002 cases of sympathectomy, no major adverse events were reported [19].

Outcomes after BCSD

Twenty patients from several reports (4 weeks to 6.5 years follow-up) suggest a 70% success rate for BCSD in suppressing severe ventricular arrhythmias. Potential adverse effects of CSD include altered temperature sensation and sweating in the face and upper extremities, and Horner's Syndrome. A major limitation with CSD has been the ability to determine acute success. Inadequate denervation may not be recognized until there is an arrhythmia recurrence. Another limitation of BCSD arises from anatomic variability of nerve pathways within and around the SC through which certain nerve fibers may still reach the heart, making CSD limited.

Future research/clinical questions

The precise mechanisms underlying SNS-induced arrhythmogenesis remain poorly understood. This area has an enormous potential impact, as ventricular arrhythmias and sudden cardiac death remain the leading causes of death in developed nations. Research questions of high impact include minimizing the invasive ness of CSD, targeting cardiac-specific sympathetic neurons and optimizing the timing of CSD, and further understanding of intra- and extra-cardiac neural remodeling. On the clinical front, improving patient selection, minimizing surgical morbidity, accurate assessment of denervation, and detailed patient follow-up and outcomes would undoubtedly improve the value of CSD in arrhythmia management.

In conclusion, the impact of cardiac sympathetic activity on ventricular arrhythmogenesis is irrefutable. In the carefully selected patient at risk of recurrent arrhythmias, BCSD may prevent the development of neural-mediated arrhythmias. Further investigation into the role of BCSD in arrhythmia prevention and treatment is warranted as the clinical impact on arrhythmias worldwide is significant.

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