Targeted stellate decentralization: Implications for sympathetic control of ventricular electrophysiology

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BACKGROUND Selective bilateral cervicothoracic sympathectomy has proven to be effective for managing ventricular arrhythmias in the setting of structural heart disease. In the procedure currently used, the caudal portions of both stellate ganglia along with thoracic chain ganglia down to T4 ganglia are removed.

OBJECTIVE The purpose of this study was to define the relative contributions of the T1–T2 and T3–T4 paravertebral ganglia in modulating ventricular electrical function.

METHODS In anesthetized vagotomized porcine subjects (n = 8), the heart was exposed via sternotomy along with right and left paravertebral sympathetic ganglia to the T4 level. A 56-electrode epicardial sock was placed over both ventricles to assess epicardial activation–recovery intervals (ARIs) in response to individually stimulating right and left stellate vs T3 paravertebral ganglia. Responses to T3 stimuli were repeated after surgical removal of the caudal portions of stellate ganglia and T2 bilaterally.

RESULTS In intact preparations, stellate ganglion vs T3 stimuli (4 Hz, 4-ms duration) were titrated to produce equivalent decreases in global ventricular ARIs (right side: 85 ± 6 ms vs 55 ± 10 ms; left side: 24 ± 3 ms vs 17 ± 7 ms). Threshold of stimulus intensity applied to T3 ganglia to achieve threshold was 3 times that of T1 threshold. ARIs in unstimulated states were unaffected by bilateral stellate–T2 ganglion removal. After acute decentralization, T3 stimulation failed to change ARIs.

CONCLUSION Preganglionic sympathetic efferents arising from the T1–T4 spinal cord that project to the heart transit through stellate ganglia via the paravertebral chain. Thus, T1–T2 surgical excision is sufficient to functionally interrupt central control of peripheral sympathetic efferent activity.

KEYWORDS Stellate ganglion; Sudden death; Sympathetic efferent neurons; Sympathectomy; Ventricular arrhythmia; Ventricular electrical indices

ABBREVIATIONS **ARI** = activation–recovery index; **dV/dt** = derived voltage; **IV** = intravenous; **LV** = left ventricle; **T1** = first paravertebral ganglion; **T3** = third paravertebral ganglion

Introduction

Sudden cardiac death affects 180,000 to 250,000 patients in the United States per year.[1] Patients with structural heart disease are at risk for ventricular arrhythmias that progress to sudden cardiac death.[1,2] Although these conditions usually can be treated with medication,[3] many are refractory to multiple medications.[2,4] Catheter ablation of select patients has proven to be an effective follow-up treatment option in many such cases.[5] Despite these approaches, there remain subsets of patients who are refractory to these therapies and experience incessant ventricular arrhythmias,[6] and some of patients have a high risk for sudden cardiac death.[4,7,8]

In those patients deemed unsuitable or unresponsive to such standard pharmacologic or ablation therapies, modulation of the autonomic nervous system is emerging as an effective adjunct therapy.[8–10] This approach is supported by recognition of the importance of the cardiac nervous system in the progression of cardiac pathologies.[2,11–13] In an emergency setting, high thoracic spinal epidural anesthesia can be used to transiently stabilize cardiac electrical function.[9] For sustained treatment, bioelectric therapies applied to the thoracic dorsal columns[10,14,15] or surgical approaches[4,7,8] applied to the paravertebral chain can modulate autonomic imbalances and reduce arrhythmias. For the surgical approach, bilateral stellate ganglion resection imparts antiarrhythmic effects in patients with refractory ventricular tachycardia.[7,8] Such a surgical procedure removes all connections from spinal cord neurons to adrenergic and other neuronal somata in the thorax. Recently, this surgical approach has been modified to surgically remove the caudal two-thirds of the stellate ganglion along with their respective paravertebral chains down to the T4 paravertebral ganglia bilaterally.[7,8] Although such surgical approaches have documented antiarrhythmic effects,[7,8] removal of T3–T4 ganglia

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frequently results in off-target adverse symptoms, such as upper thoracic and limb hyperhidrosis/hyperalgesia.[8,16–18]

Within the literature there is a fundamental discrepancy between gross anatomy and tracer-based technologies for delineating structure/function organization of central (spinal cord) to peripheral interactions for the sympathetic nervous system. Gross anatomic studies routinely depict an intrathoracic anatomy in which multiple nerves course medially to the heart from the T1 level of the paravertebral chain down to either T5 or T6 paravertebral chain ganglia.[19–23] Functional studies confirm that cardiac-related sympathetic efferent preganglionic neurons originate in the intermediolateral cell column of the spinal cord and project their axons via C7–T6 rami into the paravertebral chain.[24,25] From there, the cardiac-related preganglionic fibers project to sympathetic efferent postganglionic neuronal somata contained in the superior cervical, middle cervical, mediastinal ganglia, and stellate ganglia.[26] In contrast to most gross anatomic studies, functional studies in a canine model indicate that the primary interconnection between the stellate middle cervical and the mediastinal ganglia is via the dorsal and ventral ansae subclavian.[27]

The objective of this study was to evolve a new surgical paradigm for bilateral stellectomy that was effective in interrupting central/peripheral interactions for efferent sympathetic projections to the heart while maintaining as much of the paravertebral chain as possible. Achievement of this goal would maximize the therapeutic effects on the heart while minimizing damage to sensory and sympathetic motor control of upper limb, neck, and thoracic wall. Data from this study indicate selective removal of the T1–T2 elements of the paravertebral chain are sufficient to achieve therapeutic goals in that no sympathetic efferent fibers project from lower chain (T3–T4) ganglia to the heart except through the stellate ganglia and then via the ansae subclavia to other intrathoracic autonomic ganglia. As a corollary, by leaving the cranial portions of both stellate ganglia (inferior cervical ganglia) intact, as is done clinically,[7,8] any risk of Horner syndrome can be minimized,[28] and the major elements of intrathoracic ganglia for cardiac control can be preserved.[26] Moreover, by maintaining elements of the paravertebral chain below the stellate ganglion intact, the potential for upper limb and thoracic wall pain syndromes and hyperhidrosis can be minimized.

Methods

The study protocol was approved by the Institutional Review Board. The animal experimental protocol was performed in accordance with guidelines set by the University of California Institutional Animal Care and Use Committee and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Surgical preparation

Male Yorkshire pigs (n = 8) weighing an average of 86 ± 5 lb were tranquilized and then anesthetized with telazol (8–10 mg/kg, intramuscular) in the supine position. After endotracheal tube placement, the animals were ventilated. General anesthesia was introduced and maintained using isoflurane (1%–1.5%, inhalation) and intermittent boluses of fentanyl (50–100 μg/kg, intravenous [IV]) as required. After completion of surgery, anesthesia was changed to α-chloralose (50 mg/kg bolus followed by continuous infusion of 10 mg/kg/h). The right femoral artery was cannulated to monitor arterial blood pressure. Another catheter was inserted into the right femoral vein for fluid and drug administrations. Heart rate was monitored via limb leads. End-tidal CO_2 was maintained between 35 and 40 mm Hg. Arterial blood gas sampling was performed to ensure maintenance of adequate oxygenation. In order to maintain blood gas homeostasis, hourly adjustments were made in tidal volume along with bolus administrations of appropriate doses of sodium bicarbonate.

Median sternotomy was performed to expose the heart, the stellate ganglia, and paravertebral sympathetic chains caudal to the T4 ganglia. The cervical vagi were transected bilaterally. Thereafter, preparations were allowed to stabilize for 1 hour. At the end of each experiment, animals were euthanized by IV administration of a lethal dose of sodium pentobarbital (100 mg/kg).

Hemodynamic indices

To measure left ventricular (LV) pressure, a 5Fr pigtail associated with a 12-pole conductance catheter was inserted into the LV chamber via the left carotid artery. This device was connected to an MPVS Ultra Pressure Volume Loop System (Millar Instruments, Houston, TX). Catheter placement was confirmed using cardiac ultrasound and by examining the appropriate pressure and volume signals.

Stellate ganglion vs T3 paravertebral ganglion stimulations

The right and left stellate ganglia were stimulated individually via bipolar needle electrodes. Then the right and left T3 sympathetic chain ganglia in the paravertebral gutter were stimulated individually via bipolar needle electrodes. Bipolar electrodes were interfaced to Grass S88 stimulators (Grass Co., Warwick, RI) via SIU6 constant current stimulus isolation units. Square-wave stimulation pulses (4 Hz, 4-ms duration) were delivered individually to each site. Stimulation thresholds were defined as the stimulation current strength just sufficient to elicit a 10% increase of LV end-systolic pressure. For each stimulation site, the stimulus intensity used thereafter was 1.5 times threshold, applied for 30-second periods at 4 Hz and 4-ms duration. A 10-minute resting period was allowed between each of these stimulations.

Activation recovery index recording and analysis

A custom 56-electrode sock was placed over both ventricles to measure unipolar epicardial electrograms derived from the ventricular epicardium (Figures 1A and 1B) via a Prucka CardioLab system (GE Healthcare, Fairfield, CT).