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TARGETED STELLATE DECENTRALIZATION: IMPLICATIONS FOR SYMPATHETIC CONTROL OF VENTRICULAR ELECTROPHYSIOLOGY

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Abstract

Background—Selective, bilateral cervicothoracic sympathectomy has proven to be effective for managing ventricular arrhythmias in the setting of structural heart disease. The procedure currently employed removes the caudal portions of both stellate ganglia, along with thoracic chain ganglia down to T4 ganglia.

Objective—To define the relative contributions of T1-T2 and the T3-T4 paravertebral ganglia in modulating ventricular electrical function.

Methods—In anesthetized vagotomised 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 (ARI) in response to individually stimulating right and left stellate vs T3 paravertebral ganglia. Responses to T3 stimuli were repeated following surgical removal of the caudal portions of stellate ganglia and T2 bilaterally.

Results—In intact preparations, stellate ganglion vs T3 stimuli (4Hz, 4ms duration) were titrated to produce equivalent decreases in global ventricular ARIs (right-side 85±6 vs 55±10 ms; left-side 24±3 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. Following 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. T1-T2 surgical

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Competing interests

No authors report a conflict of interest with respect to these studies.

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excision is thus sufficient to functionally interrupt central control of peripheral sympathetic efferent activity.

Keywords

stellate ganglion; sudden death; sympathetic efferent neurons; sympathectomy; ventricular arrhythmias; ventricular electrical indices

Introduction

Sudden cardiac death affects 180,000 – 250,000 patients in the United States per year [1]. Patients with structural heart disease are at risk of ventricular arrhythmias that progress to sudden cardiac death (SCD) [1, 2]. Although these conditions can usually 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], some with a high risk for SCD [4, 7, 8].

In those patients deemed unsuitable or unresponsive to such standard pharmacological or ablation therapies, modulation of the autonomic nervous system is emerging as an effective adjunct therapy [8–10]. This approach is supported by the 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 anti-arrhythmic 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 2/3 of the stellate ganglion along with their respective paravertebral chains down to the T4 paravertebral ganglia bilaterally [7, 8]. While such surgical approaches have documented anti-arrhythmic effects [7, 8], removal of T3 –T4 ganglia 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 to delineate structure/function organization of central (spinal cord) to peripheral interactions for the sympathetic nervous system. Gross anatomical studies routinely depict an intra-thoracic anatomy where 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 (IML) cell column of the spinal cord, 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 anatomical studies, functional studies, in a canine model, indicate that the primary interconnection between the stellate, middle cervical and 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 at the same time 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], one can minimize any risk of Horner's syndrome [28] and preserve major elements of intrathoracic ganglia for cardiac control [26]. Moreover, by maintaining elements of the paravertebral chain below the stellate ganglion intact one minimizes the potential for upper limb and thoracic wall pain syndromes and hyperhidrosis

Methods

Institutional Review Board (IRB) approval was obtained for this protocol. 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 Institute of Health Guide of the Care and Use of Laboratory Animals.

Surgical preparation

Male Yorkshire pigs (n=8) weighing an average of 86±5 lbs were tranquilized and then anesthetised with telazol (8–10mg/kg, intramuscular) in the supine position. Following endotracheal tube placement, the animals were ventilated. General anaesthesia was introduced and maintained using isoflurane (1–1.5%, inhalation) and intermittent boluses of fentanyl (50–100ug/kg intravenous (iv)) as required. Following completion of surgery, anaesthesia was changed to α-chloralose (50mg/kg bolus followed by continuous infusion of 10mg/kg/hour iv). 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 35–40mmHg. Arterial blood gas sampling was performed to assure 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.

A median sternotomy was performed to expose the heart and 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 one hour. At the end of

each experiment, animals were euthanized by intravenous administration of a lethal dose of sodium pentobarbital (100 mg/kg/iv).

Hemodynamic indices

To measure left ventricular (LV) pressure, a 5-French pig tail associated with a 12-pole conductance catheter was inserted into the LV chamber via the left carotid artery. This device was connected to a 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 (LSG, RSG,) 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 left ventricular end-systolic pressure (LVESP). For each stimulation site, the stimulus intensity employed thereafter was 1.5x threshold, applied for 30 second periods at 4Hz and 4 ms duration. A 10 minute resting period was allowed between each of these stimulations.

ARI recording and analysis

A custom 56-electrode sock was placed over both ventricles to measure unipolar epicardial electrograms derived from the ventricular epicardium via a Prucka CardioLab (GE Healthcare, Fairfield, CT) system (Figure 1 A & B). Activation recovery intervals (ARIs) were calculated using customized software (ScalDyn M; University of Utah, Salt Lake City, UT). Ventricular activation times (AT) were measured from the beginning of the first derivative of derived voltage (dV/dt) in the depolarization wave of the intrinsic deflection of voltage. Ventricular electrical recovery times were measured as the time of max dV/dt to time of the peak of the repolarization wave (T wave). ARIs were then calculated as AT subtracted from RT. This index has been shown to correlate with regional ventricular action potential durations (APDs) [29, 30]. Global dispersion of repolarization (DOR) was calculated using the variance of all 56-electrode ARIs to demonstrate spatial dispersion of ventricular epicardial electrical repolarization.

Protocols

Regional ventricular epicardial electrical function and indices of LV contractility (dP/dt) were evaluated at baseline and in response to stimulation of individual stellate ganglia (right stellate stimulation: RSS or left stellate stimulation: LSS) and with corresponding same side stimulation of the T3 paravertebral sympathetic ganglia. Thereafter, the caudal ½ portion of the stellate ganglion was removed along with the chain down to and including T2 ganglia (Fig 1C). Following a 20 min recovery period, the T3 chain ganglia were re-stimulated. Similar studies were then performed on contralateral stellate and intrathoracic chain

sympathetic chain ganglia to T4. We alternated the side of the thorax in which the ganglia were first studied among animals.

Statistical analysis

Statistical analysis was performed using Sigma Stat with one-way repeated ANOVA for comparing hemodynamic and regional ventricular electrical indices before and after decentralization as well as comparing responses elicited by ganglionic stimulations in intact vs decentralized states. Paired Student's t-test and Wilcoxon rank sum were performed for comparison of continuous variables. Data so compared were considered to be statistically significant if $p<0.05$. Data are presented as mean ± SE.

Results

Chronotropic and Dromotropic Responses

Intact. In intact states, right and left-sided stellate (T1) and T3 level paravertebral chain stimuli were titrated to produce equivalent changes in heart rate and LV ARI. Overall at 4 Hz, 4 ms duration, this was achieved at 1.2±0.1 mA (RT1) vs 8.7±1.8 mA (RT3) during right-sided stimuli and 3.2±0.3 mA (LT1) vs 11.4±0.3 mA (LT3) for left-sided stimuli. Compared to baseline, right-sided stellate (RT1) stimulation increased heart rate by 39±6 beats/min ($p<0.05$) while RT3 ganglionic stimulations increased heart rate by 22±3 beats/min ($p<0.05$) (Fig. 2A). Changes in whole heart ventricular ARI from baseline were induced from RT1 [86±11ms (26±9% change); $p<0.05$) vs RT3 [55±9ms (**17**±8% change); $p<0.05$] stimulation sites (Figs 2B). There was no significant difference statistically between T1 and T3 stimulations prior to stellectomy. Figure 3 demonstrates a polar map of whole heart ARI (ms) in one animal generated from the sock electrode comparing baseline intact conditions, with right stellate ganglion stimulation (RT1) (A), right T3 stimulation in the intact (RT3) (B), and post partial stellectomy (RT3 post SGX) (C).

Compared to baseline in the intact state, while heart rate was minimally affected by left-sided stellate (LT1) or LT3 stimuli (Fig 4A), changes in whole heart ventricular ARI were induced from both sites (Fig 4B) [LT1: 24±4ms (7±3% change), $p<0.05$; LT3: 18±4ms (5±1%): $p<0.05$]. The percentage change from baseline in whole heart ARI was significant comparing stimulation pre- (intact) and post- surgical excision of the caudal stellate ganglia and adjacent T2 ganglia ($p<0.05$) (Fig 4B). Whole heart dispersions in ARI, indicative of differential patterns of sympathetic innervation, failed to show a statistical significance across right side conditions T1 vs T3 stimulation intact and post partial stellectomy (Figure 5). However, paired comparison of left-sided evoked whole heart dispersions in ARI to T3 stimulation pre- to post partial stellectomy was significant.

Chronotropic and Dromotropic Responses: Post-stellectomy

Following surgical removal of the caudal portions of the stellate ganglia and T2 paravertebral ganglion, heart rate and ventricular ARIs did not change significantly from baseline. However, following these surgical procedures, chronotropic responses to subsequent RT3 stimulations were eliminated (Fig 2A). Minimal changes in heart rate to LT3 stimulation evoked in intact state did not change post left-side stellate-T2 resection (Fig

4A). For indices of cardiac epicardial electrophysiological function (ARI, Fig 2B, 4B; ARI dispersion Fig 5), these same surgical procedures completely mitigated all functional responses to subsequent T3 level stimulations.

Hemodynamics

In intact states, stimulation of right or left stellate ganglia increased left ventricular chamber dP/dt max (right: 93%; left: 68%; $p<0.05$ from baseline) (Fig 6). Similar effects were induced in this index of ventricular contractility when T3 ganglia were stimulated (right: 71%; left: 25%: $p<0.05$ from baseline). Following ipsilateral partial stellectomy, subsequent same-sided T3 ganglion stimulation failed to enhance LV dP/dt.

Discussion

The functional data derived herein demonstrate that cardiac-related preganglionic sympathetic axons arising from the lower cervical to upper thoracic (T1-T4) spinal cord project through the paravertebral chain to the stellate ganglia and from there through the ansae subclavia to all intrathoracic cardiac-related sympathetic ganglia. In other words, there are no nerves that arise from the paravertebral sympathetic chains that project medially directly to the heart.

In the 1930s stellectomy became a treatment strategy for pain and other therapies, involving as it did on total extirpation of left-sided stellate ganglia [20, 28]. However, the results proved to be varied and the relatively extensive nature of this surgical approach frequently resulted in untoward side effects including abdominal hyperhidrosis, thoracic and upper limb pain [28]. In the 1980's, left-side stellectomy was proposed as adjunct therapy for treatment of ventricular arrhythmias [31]. This anti-arrhythmia management strategy has evolved and bilateral caudal stellectomies combined with removal of thoracic sympathetic chain ganglia down to the T4 ganglia is becoming the standard of care [8, 32, 33]. The results herein demonstrate that removal of the lower third of T1 and the T2 paravertebral ganglion is sufficient to decentralize the sympathetic paravertebral ganglia from the heart with potentially less side effects. Validation of this in human studies will be crucial to develop a simplified cardiac sympathectomy procedure given the influence of surgical excision of both stellate ganglia on reducing ventricular arrhythmias[7–9].

Anatomical-functional data is relevant when contemplating surgery involving removal of intrathoracic paravertebral sympathetic ganglia in the suppression of ventricular arrhythmias. By sparing the cranial aspects of the stellate ganglia bilaterally one minimizes the occurrence of Horner's syndrome [34] while preserving major cardiac-related neural networks localized to this same region [26]. Preserving T3 and the more caudal elements of the paravertebral chain also reduced the potential for off-target side effects such as abdominal hyperhidrosis, thoracic and upper limb pain [8, 16–18].

Functional studies demonstrate that cardiac-related preganglionic soma are localized within the intermediolateral cell column and localized to the lower cervical (C7-C8) to upper thoracic (T1-T4) spinal levels [24, 25]. These soma project axons to post ganglionic soma localized to the stellate, middle cervical, mediastinal and intrinsic cardiac ganglia [35, 36].

These ganglia each contain a complex neural network involving afferent and local circuit neurons in addition to the post-ganglionic sympathetic soma [37–40]. Together, these intrathoracic ganglia function as part of a hierarchy for cardiac control with these more peripheral elements primarily engaged in cardio-cardiac reflexes [41].

Functional data indicate that many neuronal somata in stellate ganglia are local circuit in nature – that is second order neurons that interact with one another, as well as with adrenergic motor neurons in the control of cardiac indices [42, 43]. Further, most cardiac-related motor neurons, as defined by tracer studies, are localized to the cranial aspects of the stellate ganglia [26]. Thus, removing the caudal aspects of the stellate ganglia, leaving the cranial aspects, preserves the majority of cardiac-related stellate neurons [26]. All other intrathoracic cardiac related sympathetic ganglia remain, but with their preganglionic inputs interrupted by the caudal stellectomy combined with T2 excision. This allows the system to retain capabilities for robust intrathoracic control of cardiac indices even in the chronic decentralized state [42, 43]. It is for these reasons that these surgical procedures should be considered as a surgical *decentralization* of peripheral sympathetic ganglia from central influences and not as a cardiac sympathetic *denervation*. Future studies should consider the functional capabilities of these intrathoracic reflex control loops in response to stress (e.g. orthostatic, exercise), especially in the context of adaptations that will evolve from loss of central drive. Validation of this in human studies will be crucial for a simplified cardiac sympathectomy procedure.

Limitations

The limitations of this study include the fact that responses were evaluated in an anesthetized animal model and in the short-term after surgical excision of relevant neural structures. As such, the data may not translate completely to predict the function of the human intrathoracic sympathetic nervous system. Studies were also undertaken in normal animals and as such potential cardiac disease induced changes in central-peripheral interactions for cardiac control were not evaluated. What is evident regardless of these limitations, is the positive effects on electrophysiological stability following such surgical procedures as evaluated herein, especially in the context of bilateral stellate decentralization for therapeutic management of ventricular arrhythmias [7, 8]. What is also pertinent is that these therapeutic objectives can be achieved by a more limited paravertebral excision (to T2), thus reducing the potential for off target effects that accompany excision of paravertebral ganglia caudal to that point.

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Abbreviations

ARI	Activation recovery index
SCD	Sudden Cardiac Death

IML	Intermediolateral
IRB	Institutional Review Board
IV	Intravenous
LV	Left Ventricle
LSG & RSG	Left Stellate Ganglion and Right Stellate Ganglion
LVESP	Left ventricular end systolic pressure
AT	Activation time
dV/dt	Derived voltage
APDs	Action potential duration
DOR	Dispersion of repolarization
LSS & RSS	Left stellate stimulation & Right stellate stimulation
T1 & T3	First and third paravertebral ganglion
R & L	Right and Left

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Clinical Perspective

Ventricular electrical storm may be treated with standard pharmacological therapies and ablation. In certain cases, despite our efforts, we are unable to terminate the electrical storm. In such cases, autonomic modulation with stellate decentralization is a therapy that can be considered and currently involves removal of T1-T4 of the paravertebral sympathetic chain. Clinical follow up of patients has demonstrated significant reduction in ventricular arrhythmic events with bilateral stellate decentralization but as a side effect they can experience compensatory hyperhidrosis and hyperalgesia. Manipulations of any aspect of the neural hierarchy for cardiac control have the potential to alter reflex control of the heart. In this paper, we have demonstrated in a porcine model that the T3-T4 paravertebral chain has no direct efferent connections to the heart except that which projects rostral to the stellate ganglia and from there via the ansae subclavian to the heart. This is contrary to previous understanding of the cardiac innervation from the sympathetic paravertebral ganglia based on anatomic and neural tracer studies but not functional data. We suggest that a more limited paravertebral excision (only the lower third of T1 and T2) needs to be performed to adequately decentralize peripheral aspects of the cardiac-related sympathetic nervous system from the CNS. By removing less of the sympathetic chain we expect to reduce off target side effects, thus improving patient care. Validation of this in human studies will be crucial for a simplified cardiac sympathetic decentralization procedure.

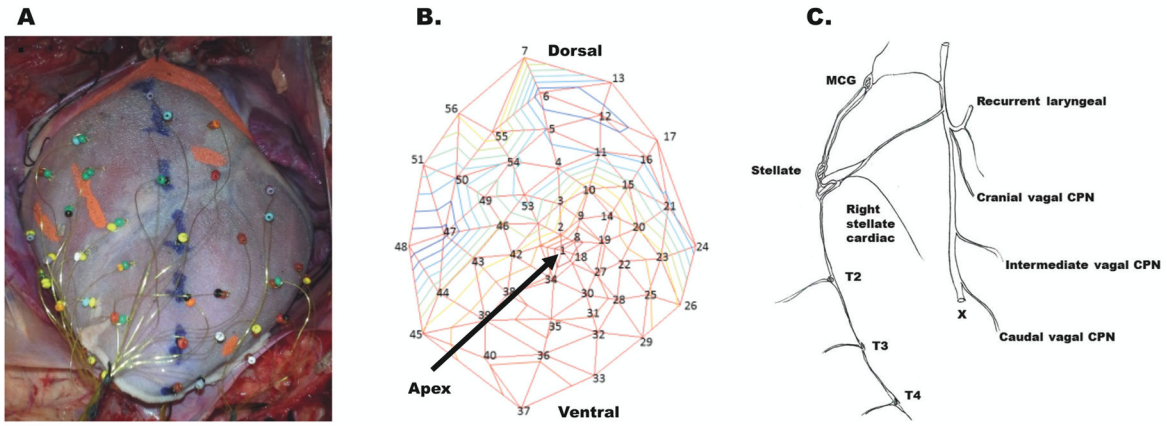

Figure 1. Recording Array and Neural Anatomy

An example of the custom 56-electrode sock placed over both ventricles to measure unipolar epicardial electrograms derived from the ventricular epicardium (B). Each electrode is color coded to correspond to a numbered specific region on the sock so that regional information can be obtained (A). Panel C schematically depicts the gross anatomical arrangement of the porcine right-sided upper thoracic paravertebral chain (T2-T4) and associated mediastinal neural structures including stellate and middle cervical (MCG) ganglia. X represents thoracic vagosympathetic trunk.

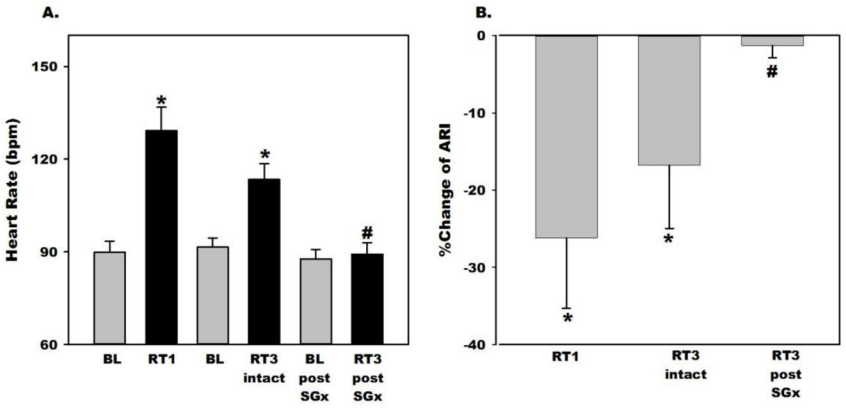

Figure 2. Heart Rate and ARI Responses to Right T1 and T3 Stimulation Pre and Post Stellectomy

Heart rate (A) and % change in ventricular ARI (B) compared to baseline (BL) in response to right-sided stellate (RT1) and T3 paravertebral (RT3) chain ganglion stimulation pre- (intact) and post- right-sided surgical excision of the caudal stellate ganglia and adjacent T2 chain ganglia (SGx). * $p<0.05$ compared to baseline; # $p<0.05$ compared to intact state.

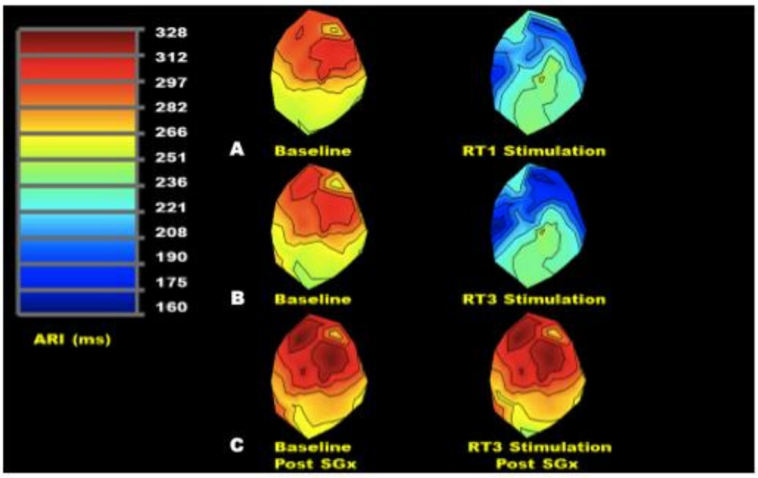

Figure 3. Cardiac ARI Maps Pre and Post Stellate Removal

An example of polar maps of ARI (ms) in one animal, generated from the sock electrode, are shown comparing baseline intact conditions, with right stellate ganglion stimulation (RT1) (A) and right T3 stimulation in the intact (RT3) state (B), vs. T3 stimulation post partial stellectomy (RT3 post SGx) (C). There is significant ARI shortening with RT1 and RT3 stimulation in the intact condition. When RT3 is stimulated post partial stellectomy there is no significant change in ARI from baseline.

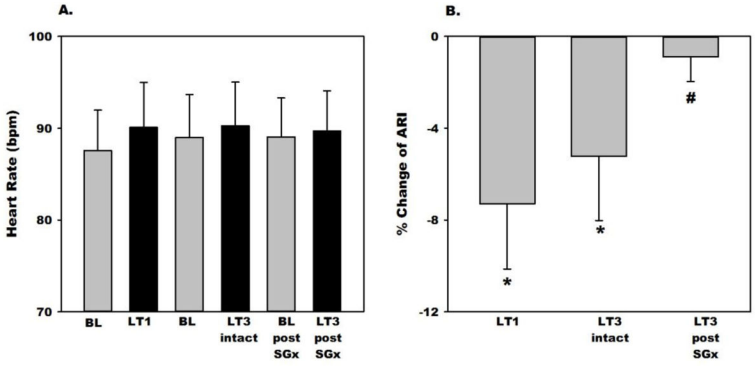

Figure 4. Heart Rate and ARI Responses to Left T1 and T3 Stimulation Pre and Post Stellectomy

Heart rate (A) and % change in ventricular ARI (B) compared to baseline (BL) in response to left sided stellate (LT1) and T3 paravertebral (LT3) chain ganglion stimulation pre- (intact) and post- left-sided surgical excision of the caudal stellate ganglia and adjacent T2 chain ganglia (SGx). * $p<0.05$ compared to baseline; # $p<0.05$ compared to intact state.

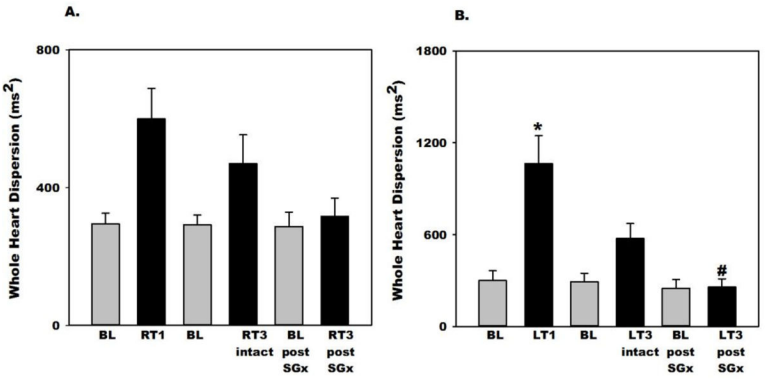

Figure 5. Dispersion of Repolarization in Response to T1 and T3 Stimulation Pre and Post Stellectomy

Whole heart dispersion (ms^2) for right (A) and left (B) T1 and T3 stimulation compared to baseline (BL) in the intact vs post partial stellectomy (SGx) state. * $p<0.05$ compared to baseline; # $p<0.05$ compared to intact LT3 stimulation.

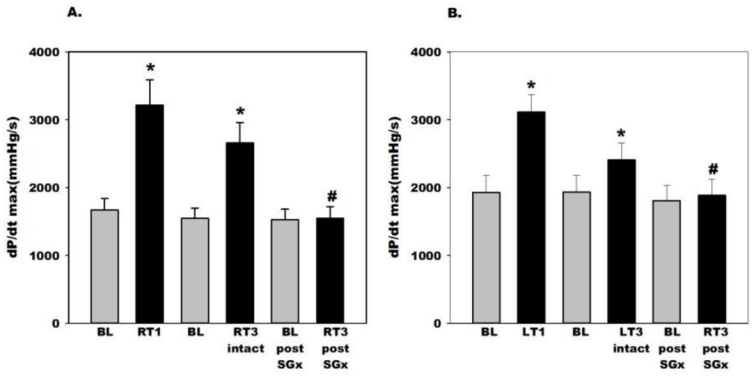

Figure 6. Ventricular dP/dt responses to Right and Left T1 and T3 Stimulation Pre and Post Stellectomy

Change in right ventricular dP/dt maximum in response to right-sided (panel A) and left-sided (panel B) T1 and T3 stimulation compared to baseline (BL) in intact state and following surgical excision of the caudal stellate ganglia and adjacent T2 chain ganglia (SGx). * $p<0.05$ compared to baseline; # $p<0.05$ compared to intact state.