

Effects of Stepwise Denervation of the Stellate Ganglion: Novel Insights from an Acute Canine Study

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Abstract

Background: The stellate ganglion (SG) is important for cardiac autonomic control. SG modification is an option for treating refractory ventricular tachyarrhythmias. The optimal extent of left- and right-sided SG denervation necessary for antiarrhythmic effect, however, remains to be learned.

Objective: To evaluate the effects of stepwise SG denervation on hemodynamic and electrophysiologic parameters in dogs.

Methods: After sequential left and right thoracotomy in 8 healthy dogs, the SG was exposed by dissection. Two pacing wires were placed in the upper SG to deliver high-frequency stimulation. The lower SG, ansae subclaviae, and upper SG were removed in a stepwise manner. The same protocol was performed on the right side. Blood pressure (BP), heart rate, and electrophysiologic parameters were recorded at baseline and after 5 minutes of stimulation.

Results: Systolic and diastolic BP significantly increased during upper left SG stimulation. Mean increase in systolic BP from baseline was 49.4 (26.6) mm Hg ($P=.007$), 25.5 (14.1) mm Hg after the lower SG was removed ($P=.02$), and 8.6 (3.4) mm Hg after resection of the ipsilateral ansae subclaviae ($P=.048$). Heart rate and other electrophysiologic parameters did not change significantly. After complete removal of the left SG, the systolic BP increased 34.0 (17.6) mm Hg ($P=.005$) after stimulation of the right SG.

Conclusions: Sympathetic output remains after the lower SG is removed, and sympathetic output from the right SG remains after complete resection of the left SG

and ansae subclaviae. Thus, some patients who undergo left SG denervation can still have significant sympathetic response via right SG regulation.

Key Words: ansa subclavia; canine; cardiac sympathetic denervation; stellate ganglion; vagal trunk

Abbreviations

BP, blood pressure

CSD, cardiac sympathetic denervation

ERP, effective refractory period

HR, heart rate

LSG, left side of the SG

LV, left ventricle

RSG, right side of the SG

SG, stellate ganglion

VF, ventricular fibrillation

VT, ventricular tachyarrhythmia

Introduction

The heart is richly innervated by autonomic nerves. The balance between the parasympathetic and sympathetic effects of the autonomic nervous system has an important role in proper cardiac function.¹ Both aspects of the autonomic nervous system have significant effects on cardiac chronotropy and inotropy.² The stellate ganglion (SG) provides important sympathetic nerve inputs into the heart and may predispose the myocardial conduction system and myocardium itself to multiple types of atrial and ventricular arrhythmias.³

Cardiac sympathetic denervation (CSD) has been shown to reduce the burden of ventricular arrhythmias acutely.⁴ Preganglionic sympathetic efferents arising from the T1-T4 spinal cord that project to the heart transit through stellate ganglia via the paravertebral chain. In left-sided CSD procedures, the lower half (T1-T4) of the left side of the SG (LSG) is removed.⁵ A recent work by Buckley and Ardell showed that T1-T2 surgical excision is sufficient to functionally interrupt central control of peripheral sympathetic efferent activity.⁶ However, the upper part of T1 of the LSG and ansae subclaviae remain connected to the heart and can still affect cardiac function through these remaining sympathetic innervations. Studies defining the role of the remaining segments after left CSD are scarce. Furthermore, the balance between the sympathetic and parasympathetic nervous systems is dynamic and is altered after left CSD procedures. Thus, we investigated the effects of stepwise SG denervation with subsequent stimulation of the remaining nerve tissue in dogs to assess the physiologic effects on blood pressure (BP), heart rate (HR), and electrophysiologic intervals.

Methods

Animal Preparation and Anesthesia

The study were approved by the Mayo Clinic Institutional Animal Care and Use Committee and performed under the guidelines of the National Institutes of Health Guide for the Care and Use of Animals. 8 male mongrel dogs (weight, 30-40 kg) were anesthetized with ketamine/diazepam for induction and intubation, and intravenous isoflurane (1%-3%) and propofol (7-15 mg/kg per min) were used to provide adequate anesthesia during nerve stimulation, as well as for maintenance of an adequate anesthetic plane during thoracotomy to access the nervous structures. After visualization of these structures, isoflurane was reduced to the lowest level possible, and propofol was increased to maintain adequate anesthesia. This was done to allow for adequate evaluation of the sympathetic system during stimulation testing, because propofol has less effect on autonomic tone than isoflurane.^{7, 8}

HR and heart rhythm were monitored continuously throughout the study. BP was monitored continuously via a femoral arterial line and was recorded at 15-minute intervals when not measured as part of the stimulation aspect of the study. Core body temperature was monitored and maintained euthermic throughout the study. Vascular access was obtained percutaneously, and sheaths were placed using an over-the-wire technique. Femoral veins, arteries, and external jugular veins were used for placement of 9 to 12 F sheaths for access for the monitoring and stimulation electrodes.

Catheter Placement for Electrophysiologic Study

A Boston Scientific XPT Blazer II Catheter (8 F, 4-mm tip, 2.5-mm electrode spacing) was placed at the right ventricular apex for both ventricular recording and stimulation. A multipolar catheter (CS catheter, 6F; Biosense Webster) was inserted into

the internal jugular vein and placed in the coronary sinus under fluoroscopic guidance (Axiom artis dTA; Siemens Inc). Electrocardiography, arterial BP, and multichannel intracardiac electrograms were continuously stored using the Prucka CardioLab recording system (GE Healthcare).

Electrophysiology parameters were collected from the Prucka system using coronary sinus and ventricular recording catheters. These included the PR, QRS, and QT intervals. Pacing from the coronary sinus and right ventricle was done using a Bloom Stimulator (Fischer Medical Technologies LLC). The atrial and ventricular effective refractory periods (ERPs) were determined by pacing the left atrium and right ventricle, noting the refractory period from a drive train of 8 pulses with a subsequent early S2 stimulus at twice the pacing threshold of the tissue. The left atrial conduction time was taken as the time for signal travel from the distal to proximal coronary sinus when the left atrium was captured. The left ventricular (LV) conduction time was determined as the traveling time from distal to proximal coronary sinus when the LV was captured.

Approach to Thoracotomy and Nerve Dissection

The methods of thoracotomy and nerve dissection have been previously reported in detail.⁹⁻¹¹ In brief, thoracotomy was performed through the left 3rd intercostal space. The pericardium was opened to expose the left atrial appendage and the base of the LV. The LSG, vagal trunk, and left ansae subclaviae were identified (Figure 1A). After the left-sided procedure and protocol was completed, the wound was closed and a similar surgical procedure was performed on the right side via thoracotomy through the

right 3rd intercostal space. The right side of the SG (RSG), right vagal trunk, and right ansae subclaviae were then identified (Figure 1B).

Experimental Procedure and Stimulation Sequence

A standard Grass Stimulator (Grass Technologies) with a 10-Hz, 2-ms pulse duration and 10-V output was connected directly to the nervous structures via a pair of electrically active epicardial pacing suture wires. Before and after stimulation, electrophysiologic and hemodynamic measurements were recorded.

The process of nerve dissection and stimulation is illustrated in Figure 2. The stimulation sequence included the initial stimulation of the intact LSG. Recordings were taken at baseline and 5 minutes after continuous stimulation. The left vagal trunk was stimulated next. Thereafter, the lower half of the LSG along with T2-T3 was resected. The stimulation wires were placed into the upper half of the LSG, and stimulation recordings were then performed. Subsequently, the left ansae subclaviae was severed, and we repeated our stimulation protocol. After this step, complete LSG dissection was performed and the stimulation wires were placed into ganglion chain just above SG and stimulated. Then the left-sided chest wound was closed, and the same process was repeated on the right side.

Statistical Analyses

All measurement data are expressed as mean (SD). Paired values before and after stimulations were compared using paired *t* tests. *P* values <.05 were considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0, SPSS, Inc).

Results

Baseline Stimulation of Left- and Right-Sided Nerves

In dogs with an intact SG, the systolic and diastolic BP significantly increased during LSG stimulation (Table 1). We found an average increase from baseline of 49.4 (26.6) mm Hg for systolic BP ($P=.007$) and 33.1 (18.9) mm Hg for diastolic BP ($P=.008$). Despite the increase in BP, the average heart rate did not change significantly ($P=.35$). In addition, no significant changes were seen in the atrial or ventricular ($P=.09$) ERPs, atrial conduction time, or other electrophysiologic parameters (Table 1).

When the left vagal trunk was stimulated, the systolic BP decreased by 18.6 (11.3) mm Hg from baseline, but this change was not statistically significant ($P=.09$). However, the diastolic BP significantly decreased by 11.8 (6.2) mm Hg ($P=.002$). Furthermore, the average HR decreased by 24 beats/min ($P=.04$) and atrial ERP was shortened by 17.6 (13.9) ms ($P=.04$) (Table 1).

Stimulation of the RSG after removal of the LSG and the left ansae subclaviae led to significant increases in both systolic BP (by 34.0 (17.6) mm Hg; $P=.005$) and diastolic BP (by 13.0 (10.7) mm Hg; $P=.005$). The HR increased significantly by an average of 24 beats/min ($P=.03$), and the atrial ERP was significantly shortened, with an average decrease of 37.7 (5.5) ms ($P=.001$) (Table 1).

When the right vagal trunk was stimulated, average HR decreased significantly, by 25.0 (10.2) beats/min ($P=.04$) (Table 1). The extent of HR reduction was not significantly different between the left and right vagal trunk stimulations (-29.0 [21.5] vs -25.0 [14.1] beats/min, respectively; $P=.62$).

Effects of Stepwise Denervation

After resection of the lower half of the LSG, the systolic and diastolic BP were still susceptible to significant increase with stimulation, but to a lesser extent compared with the intact LSG (Table 2). The average increases in systolic and diastolic BP from before to after stimulation were 25.5 (14.1) mm Hg and 16.2 (11.8) mm Hg, respectively (both $P=.02$). No significant changes were noted in HR or other electrophysiologic parameters comparing prestimulation and poststimulation values.

After the left ansa subclavia was resected from the remaining LSG, the average poststimulation increase in systolic BP was 8.6 (3.4) mm Hg from pre stimulation ($P=.047$), and the increase in diastolic BP was 8.8 (3.9) mm Hg ($P=.02$). No significant changes were seen in HR or other electrophysiologic parameters (Table 2). After complete removal of the LSG and ansae subclaviae, there were no significant changes in HR, BP, QT interval, PR interval, R-R interval, atrial ERP, ventricular ERP, or left atrial conduction time compared with prestimulation values (Table 2).

Effects of Stepwise Right Denervation

After removal of the lower half of the RSG and ansae subclaviae, no significant changes in any hemodynamic or electrophysiologic parameters were noted by stimulating the upper RSG (Table 3).

Comparing Magnitude of BP Effect after Stepwise Denervation

We compared the delta values for change in systolic BP at each step in the denervation process and found that the extent of effect on BP by SG stimulation differed. In our left-sided denervation protocol, the mean (SD) change in systolic BP from pre stimulation to post stimulation of the LSG was 49.3 (18.9) mm Hg; it was 25.5 (9.5) mm Hg after dissecting the lower half of the LSG, 8.6 (8.0) mm Hg post denervation of the

left ansa subclavia, and 3.1 (2.9) mm Hg after total removal of the LSG. All delta values for systolic BP were significantly lower than in the previous step (Figure 3A). In the right-sided denervation protocol, the mean delta values for systolic BP were 33.0 (12.1) mm Hg for the intact RSG, 13.8 (26.1) mm Hg after denervation of the lower RSG, 0.2 (14.5) mm Hg post denervation of the right ansa subclavia, and 3.25 (8.3) mm Hg after complete removal of the RSG (Figure 3B).

Discussion

Response to Stimulation of Thoracic Cardiac Nerves

We found that stimulation of the left or right SG had significant effects on BP but no significant effects on the electrocardiographic conduction intervals, atrial and ventricular conduction times. In addition, right SG stimulation, but not left, increased HR. The increase in BP could be associated with an increase in cardiac contractile force and/or peripheral vascular resistance, as demonstrated in previous studies.^{12, 13} In those studies, stimulation of the LSG or RSG appears to induce positive inotropic changes and significantly increase intramyocardial pressure, systolic epicardial coronary venous pressure, and systolic coronary venous flow. Stimulation of the left ansa subclavia or ventrolateral nerve also resulted in a significant ventricular positive inotropic response.

The magnitude of the increase in BP appears to be greater with LSG stimulation than RSG stimulation, consistent with the LSG being thought to dominate cardiac sympathetic control. Furthermore, the RSG has an independent effect on BP regulation after the LSG is completely resected. This observation is consistent with the previous

findings which demonstrated a similar increase in ventricular interstitial norepinephrine level by LSG or RSG stimulation. ^{14 15}

RSG stimulation increased HR, but LSG stimulation did not, which suggests that the RSG predominantly innervates the sinus node and thus affects HR regulation. Intuitively, the increase in BP by manipulation of the RSG could result from an increased positive inotropic force and/or increased HR. Both inotropic and chronotropic effects increase cardiac output and therefore, the BP. Ajjola et al¹⁶ reported a study on percutaneous stimulation of the lower LSG in humans. Similar to our study, they found that LSG stimulation did not affect HR but did increase BP and dP/dt max. They also found that the corrected QT interval and T-wave duration and amplitude were not changed significantly, findings that were echoed in our study. **We found SG stimulation had a trend, but nonsignificant reduction in VERP, not consistent with previous reports.** ^{6, 14, 17, 18} **One explanation is the difference of our stimulation protocol and the site of stimulation from other studies. Alternatively, high background sympathetic tone of the experimental model associated with anesthesia and bilateral thoracotomy may mask the effect of SG stimulation on myocardial repolarization.**

Stimulation of either side of the vagal trunk decreases HR, a well-known physiologic effect. In our study, the extent of HR reduction appears to be similar between left and right vagal stimulation. This finding is consistent with results recently reported by Yamakawa et al.¹⁹

Effects of Stepwise Sympathetic Denervation

We found a gradation in the extent of BP increase that occurred during stimulation of the SG after dissection of each of its components. The magnitude of BP increase was lessened, but still significant, after removing the lower half of the LSG down to the T3 level. Anatomically, as we directly observed, the ansae subclaviae directly connect between the upper part of the SG and the vagal trunk, as shown in Figure 1, or branch out, innervating the heart. They have a strong sympathetic output, as demonstrated by Norris et al.²⁰

We observed that the ansae subclaviae directly innervate the vagal trunk, as reported previously.^{18, 21, 22} Sheikh-Zade et al reported that in acute experiments on cats, stimulation of the ansae subclaviae potentiated the effects of vagal stimulation. The fibers of the ansae subclaviae that insert into the vagal trunk may affect vagal-sympathetic interactions in the heart.²³ After the ansae subclaviae were resected, a modest BP response remained. This may indicate that sympathetic fibers of the upper SG distribute to the myocardium via other potential connections, which can be a source of sympathetic-related arrhythmia after permanent SG-T4 denervation in patients with ventricular arrhythmia.

Although right-sided SG stimulation increases BP, removal of the right lower SG appeared to eliminate the sympathetic effect on BP response. This differs from left-sided SG denervation, in which the increase in BP remained until the entire SG and ansae subclaviae were removed. We could speculate that the right upper SG and ansae subclaviae have less control over the canine myocardium.

We also found that the RSG had a significant and independent effect even after LSG denervation. The innervation of the LV from the RSG and the effects of the RSG

on cardiac arrhythmia are still controversial.^{14, 24} Previous studies have shown predominantly that the RSG innervates the anterior aspect of the ventricles, whereas the LSG predominantly affects the posterior aspect.^{17,25} The left-sided cardiac sympathetic innervations has been considered quantitatively dominant at the ventricular level as an arrhythmogenic source.²⁶ However, recent studies have indicated that the RSG also has an important role in cardiac function. Opthof et al²⁷ found significant inter-animal variability in the average VF interval between local activations during SG stimulation and indicated that the LSG did not significantly innervate the anterior LV wall. Vaseghi et al¹⁴ found that both the LSG and RSG provided significant innervation to the anterior LV wall. These studies, as well as our data, suggest that bilateral sympathetic denervation may be required to reduce ventricular arrhythmia.

Extent of SG Denervation and Clinical Implications

Lower half LSG denervation has been shown to be effective in treating malignant ventricular arrhythmia in congenital long QT syndrome, catecholaminergic polymorphic VT, and acquired malignant ventricular arrhythmias with or without structural heart diseases.²⁸⁻³¹ However, some patients still have recurrent arrhythmias after this procedure.^{32 33} Our findings suggest that sympathetic output remains effective even after the lower half LSG is removed. Left ansae subclaviae, and left upper SG maintains independent sympathetic effect, potentially responsible for sympathetic mediated VT/VF. The right SG is also an independent sympathetic target for treating drug-refractory VT/VF. These findings are supportive to the report from Vaseghi et al⁴ who found bilateral CSD to be more beneficial than left CSD alone.

Study Limitations

Propofol was used as anesthetic in this study. Although propofol may have less of an impact on autonomic function compared to isoflurane, it is a cardio-depressant, and its effects on hemodynamics may exist. We did stepwise dissection of different portion of SG. Yet the lower stellate ganglion, ansae subclaviae and upper stellate ganglion are not distinct entities and it is almost impossible to identify single structures and separate afferent and efferent fibers within the same structure. The RSG was stimulated only after LSG was completely resected. Thus, there was no direct comparison between intact LSG vs. intact RSG stimulation. This limitation may impact on the magnitude of effect on RSG stimulation. Finally, the study did not attempt to assess ventricular or atrial vulnerability by programmed electrical stimulation. The assessment of myocardial vulnerability could support the concept that lower stellate ganglion ablation only, as it is commonly performed in the clinical setting, may have important limitations on the effect of sympathetic denervation.

Conclusions

Sympathetic output remains even after removal of the lower half of the LSG with intact ansa subclavia in dogs. This finding may partially explain some of the incomplete success in patients undergoing unilateral LSG denervation for treating ventricular arrhythmias. In addition, although the LSG has a dominant role in the autonomic control of cardiac physiology, the RSG seems to be an additional and independent sympathetic target for treating ventricular tachyarrhythmias.

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References

1. Lympopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: Pathophysiology and therapy. *Circ Res.* 2013;113:739-753
2. Hellyer J, George Akingba A, Rhee KS, Tan AY, Lane KA, Shen C, Patel J, Fishbein MC, Chen PS. Autonomic nerve activity and blood pressure in ambulatory dogs. *Heart Rhythm.* 2014;11:307-313
3. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: Pathophysiology and therapy. *Circ Res.* 2014;114:1500-1515
4. Vaseghi M, Gima J, Kanaan C, Ajjola OA, Marmureanu A, Mahajan A, Shivkumar K. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up. *Heart Rhythm.* 2014;11:360-366
5. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long qt syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm.* 2009;6:752-759
6. Buckley U, Yamakawa K, Takamiya T, Andrew Armour J, Shivkumar K, Ardell JL. Targeted stellate decentralization: Implications for sympathetic control of ventricular electrophysiology. *Heart Rhythm.* 2015;14:022
7. Madhavan M, Desimone CV, Ebrille E, Mulpuru SK, Mikell SB, Johnson SB, Suddendorf SH, Ladewig DJ, Gilles EJ, Danielsen AJ, Asirvatham SJ. Transvenous stimulation of the renal sympathetic nerves increases systemic blood pressure: A potential new treatment option for neurocardiogenic syncope. *J Cardiovasc Electrophysiol.* 2014;25:1115-1118
8. DeSimone CV, Ebrille E, Syed FF, Mikell SB, Suddendorf SH, Wahnschaffe D, Ladewig DJ, Gilles EJ, Danielsen AJ, Holmes DR, Asirvatham SJ. Novel balloon catheter device with pacing, ablating, electroporation, and drug-eluting capabilities for atrial fibrillation

- treatment--preliminary efficacy and safety studies in a canine model. *Transl Res.* 2014;164:508-514
9. Choi EK, Shen MJ, Han S, Kim D, Hwang S, Sayfo S, Piccirillo G, Frick K, Fishbein MC, Hwang C, Lin SF, Chen PS. Intrinsic cardiac nerve activity and paroxysmal atrial tachyarrhythmia in ambulatory dogs. *Circulation.* 2010;121:2615-2623
 10. Ulphani JS, Arora R, Cain JH, Villuendas R, Shen S, Gordon D, Inderyas F, Harvey LA, Morris A, Goldberger JJ, Kadish AH. The ligament of marshall as a parasympathetic conduit. *Am J Physiol Heart Circ Physiol.* 2007;293:H1629-1635
 11. Lin J, Scherlag BJ, Lu Z, Zhang Y, Liu S, Patterson E, Jackman WM, Lazzara R, Po SS. Inducibility of atrial and ventricular arrhythmias along the ligament of marshall: Role of autonomic factors. *J Cardiovasc Electrophysiol.* 2008;19:955-962
 12. Norris JE, Randall WC. Responses of the canine myocardium to stimulation of thoracic cardiac nerves. *Am J Physiol.* 1977;232:H485-494
 13. Armour JA, Klassen GA. Pressure and flow in epicardial coronary veins of the dog heart: Responses to positive inotropism. *Can J Physiol Pharmacol.* 1984;62:38-48
 14. Vaseghi M, Zhou W, Shi J, Ajjola OA, Hadaya J, Shivkumar K, Mahajan A. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. *Heart Rhythm.* 2012;9:1303-1309
 15. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, Bloise R, De Ferrari GM, Klersy C, Moss AJ, Zareba W, Robinson JL, Hall WJ, Brink PA, Toivonen L, Epstein AE, Li C, Hu D. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-qt syndrome. *Circulation.* 2004;109:1826-1833
 16. Ajjola OA, Howard-Quijano K, Scovotti J, Vaseghi M, Lee C, Mahajan A, Shivkumar K. Augmentation of cardiac sympathetic tone by percutaneous low-level stellate ganglion stimulation in humans: A feasibility study. *Physiol Rep.* 2015;3

17. Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles. Production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. *Circ Res.* 1966;18:416-428
18. Ramirez RJ, Ajjola OA, Zhou W, Holmstrom B, Luning H, Laks MM, Shivkumar K, Mahajan A. A new electrocardiographic marker for sympathetic nerve stimulation: Modulation of repolarization by stimulation of stellate ganglia. *J Electrocardiol.* 2011;44:694-699
19. Yamakawa K, So EL, Rajendran PS, Hoang JD, Makkar N, Mahajan A, Shivkumar K, Vaseghi M. Electrophysiological effects of right and left vagal nerve stimulation on the ventricular myocardium. *Am J Physiol Heart Circ Physiol.* 2014;307:H722-731
20. Norris JE, Lippincott D, Wurster RD. Responses of canine endocardium to stimulation of the upper thoracic roots. *Am J Physiol.* 1977;233:H655-659
21. Onkka P, Maskoun W, Rhee KS, Hellyer J, Patel J, Tan J, Chen LS, Vinters HV, Fishbein MC, Chen PS. Sympathetic nerve fibers and ganglia in canine cervical vagus nerves: Localization and quantitation. *Heart Rhythm.* 2013;10:585-591
22. Rhee KS, Hsueh CH, Hellyer JA, Park HW, Lee YS, Garlie J, Onkka P, Doytchinova AT, Garner JB, Patel J, Chen LS, Fishbein MC, Everett Tt, Lin SF, Chen PS. Cervical vagal nerve stimulation activates the stellate ganglion in ambulatory dogs. *Korean Circ J.* 2015;45:149-157
23. Sheikh-Zade YR, Cherednik IL, Galenko-Yaroshevskii PA, Mukhambetaliev G. Sympathetic modulation of vagal chronotropic and arrhythmogenic influences on the heart. *Bull Exp Biol Med.* 2002;133:535-537
24. Zhou W, Yamakawa K, Benharash P, Ajjola O, Ennis D, Hadaya J, Vaseghi M, Shivkumar K, Mahajan A. Effect of stellate ganglia stimulation on global and regional left ventricular function as assessed by speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol.* 2013;304:H840-847

25. Schwartz PJ, Snebold NG, Brown AM. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. *Am J Cardiol.* 1976;37:1034-1040
26. Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. *Nat Rev Cardiol.* 2014;11:346-353
27. Opthof T, Misier AR, Coronel R, Vermeulen JT, Verberne HJ, Frank RG, Moulijn AC, van Capelle FJ, Janse MJ. Dispersion of refractoriness in canine ventricular myocardium. Effects of sympathetic stimulation. *Circ Res.* 1991;68:1204-1215
28. Coleman MA, Bos JM, Johnson JN, Owen HJ, Deschamps C, Moir C, Ackerman MJ. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-qt syndrome. *Circ Arrhythm Electrophysiol.* 2012;5:782-788
29. Olde Nordkamp LR, Driessen AH, Odero A, Blom NA, Koolbergen DR, Schwartz PJ, Wilde AA. Left cardiac sympathetic denervation in the netherlands for the treatment of inherited arrhythmia syndromes. *Neth Heart J.* 2014;22:160-166
30. Hofferberth SC, Cecchin F, Loberman D, Fynn-Thompson F. Left thoracoscopic sympathectomy for cardiac denervation in patients with life-threatening ventricular arrhythmias. *J Thorac Cardiovasc Surg.* 2014;147:404-409
31. He D, Costello JP, Nadler EP, Moak JP, Jonas RA, Nath DS. Left thoracoscopic sympathectomy used as primary therapy for a young child with intractable long qt syndrome. *Pediatr Cardiol.* 2013;34:1969-1971
32. Bos JM, Bos KM, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation in long qt syndrome: Analysis of therapeutic nonresponders. *Circ Arrhythm Electrophysiol.* 2013;6:705-711
33. Wong CW, Wang CH, Wen MS, Yeh SJ, Wu D. Effective therapy with transthoracic video-assisted endoscopic coagulation of the left stellate ganglion and upper sympathetic trunk in congenital long-qt syndrome. *Am Heart J.* 1996;132:1060-1063

Figure legends

Figure 1. Anatomy of Stellate Ganglion, Vagal Trunk, and Ansa Subclaviae.

A, Left stellate ganglion (LSG), left vagal trunk, and left ansa subclavia. B, Right stellate ganglion (RSG), right vagal trunk, and right ansa subclavia.

Figure 2. Illustration of Nerve Dissection and Stimulation.

Left figure illustrates stellate ganglion (SG), T2 and Anca (ansa subclavian) connecting to the vagal nerve. ① indicates lower half SG, ② ansa subclavia, ③ upper half SG.

Right figure shows removal of lower half SG (B), Anca (C) and upper half SG (D).

The nerve dissection algorithm is shown on the very right.

Figure 3. Comparison of Change (Delta) in Systolic Blood Pressure (BPS) With Stepwise Denervation.

A, Comparison of the delta value of BPS for left-sided stepwise denervation. Total stellate ganglion (SG) stimulation at baseline, then after the lower SG was cut, ansae subclaviae cut, and SG completely cut in stepwise manner; there was a gradation of effects on BPS. B, Comparison of the delta BPS for right-sided stepwise denervation. Only the second step, lower half SG cut had significant decrease in delta BPS. There were no significant differences between the latter 3 steps.

Table 1. Effects of Baseline Stimulation^a

Measure	Left SG (n=8)		Left Vagal Trunk (n=8)		Right SG (n=6)		Right Vagal Trunk (n=6)	
	Pre stim	Post stim	Pre stim	Post stim	Pre stim	Post stim	Pre stim	Post stim
HR, beats/min	121.3 (16.1)	127.7 (14.1)	126.6 (11.2)	97.6 (25.3) ^b	125.2 (11.2)	149.2 (17.7) ^b	128.0 (12.0)	103.0 (23.0) ^b
BPS, mm Hg	123.3 (22.2)	172.7 (36.3) ^b	131.3 (18.8)	112.5 (25.8)	117.7 (24.3)	150.7 (33.7) ^c	113.5 (18)	100.0 (21.7)
BPD, mm Hg	72.9 (19.7)	106.0 (16.0) ^b	81.6 (11.8)	69.8 (9.2) ^c	74 (17.5)	87 (29.0) ^c	71.5 (7.18)	61.75 (9.0)
AERP, ms	147.5 (19.8)	138.7 (19.6)	143.3 (17.5)	125.7 (23.7) ^b	161.7 (17.2)	134.0 (19.5) ^c	152.5 (15)	137.5 (37.7)
VERP, ms	176.3 (14.1)	170.0 (15.1)	175.0 (10.5)	171.4 (9.0)	168.3 (17.2)	161.7 (14.7)	160.0 (8.2)	172.5 (29.9)
R-R interval, ms	497.1 (63.4)	476.3 (46.5)	449.4 (50.6)	635.7	484.5	415.8 (62.5)	471.0	611.5

				(288.0)	(49.4)		(33.5)	(138.1)
PR interval, ms	111.4 (14.8)	108.0 (18.2)	102.6 (16.1)	113.0 (36.0)	118 (12.6)	96.7 (26.2)	121.25 (3.9)	123.3 (16.0)
QRS, ms	61.0 (4.5)	61.3 (4.6)	62.3 (50.2)	64.4 (8.8)	61.8 (4.6)	59.7 (5.5)	63 (8.6)	63 (7.0)
QT interval, ms	254.0 (20.9)	242.9 (12.9)	243.1 (12.5)	257.1 (16.9)	250.7 (24.1)	235.3 (22.4)	237.5 (9.5)	253.5 (17.5) ^b
LA conduction, ms	25.6 (10.2)	24.0 (8.6)	22.4 (10.3)	23.7 (11.0)	25.2 (10.6)	21.7 (7.4)	32 (9.8)	24.5 (11.4)

Abbreviations: AERP, atrial effective refractory period; BPD, diastolic blood pressure; BPS, systolic blood pressure; HR, heart rate; LA, left atrial; LV, left ventricular; SG, stellate ganglion; stim, stimulation; VERP, ventricular effective refractory period.

^a All values are mean (SD).

^b $P < .05$ vs prestimulation value.

^c $P < .01$ vs prestimulation value.

Table 2. Effects of Stepwise Left Sympathetic Denervation^a

Measure	Lower Half SG Cut (n=7)		Ansa Subclaviae Cut (n=5)		SG Completely Cut (n=6)	
	Pre stim	Post stim	Pre stim	Post stim	Pre stim	Post stim
HR, beats/min	121.7 (15.6)	122.9 (19.6)	126.4 (18.3)	129.4 (20.9)	130.6 (20.0)	135.2 (22.2) ^b
BPS, mm Hg	113.5 (14.8)	139.0 (20.4) ^b	114.8 (16.0)	123.4 (18.7) ^b	115.5 (23.4)	118.6 (27.4)
BPD, mm Hg	67.3 (13.2)	83.5 (19.0) ^b	68.2 (10.1)	77.0 (13.4) ^b	68.3 (18.9)	70.8 (19.5)
AERP, ms	140.0 (12.6)	133.3 (12.1)	140.0 (10.0)	146.0 (13.4)	146.6 (16.3)	150.0 (12.2)
VERP, ms	172.9 (13.8)	164.3 (7.9)	172.0 (8.4)	174.0 (13.4)	173.3 (8.2)	174.0 (5.5)
R-R interval, ms	484.3 (73.1)	492.9 (75.7)	476.4 (78.3)	468.0 (80.3)	467.0 (70.4)	453.6 (77.3)
PR interval, ms	109.3 (22.1)	106.5 (10.9)	113.0 (9.1)	112.8 (10.2)	112.0 (10.7)	113.6 (8.8)
QRS, ms	60.9 (3.4)	58.4 (3.2)	60.6 (4.0)	65.2 (14.7)	61.7 (4.5)	57.6 (2.7) ^b
QT interval, ms	246.0 (16.9)	236.8 (19.6)	241.8 (23.1)	242 (26.5)	240.8 (20.8)	239.8 (27.9)

LA conduction,	24.9 (9.0)	20.7 (8.1)	25.6 (7.8)	25.2 (7.8)	26.3 (6.8)	26.4 (5.9)
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ms

Abbreviations: AERP, atrial effective refractory period; BPD, diastolic blood pressure; BPS, systolic blood pressure; HR, heart rate; LA, left atrial; LV, left ventricular; SG, stellate ganglion; stim, stimulation; VERP, ventricular effective refractory period.

^a All values are mean (SD).

^b $P < .05$ vs prestimulation value.

Table 3. Effects of Stepwise Right Sympathetic Denervation^a

Measure	Lower Half SG Cut		Ansa Subclaviae Cut		SG Completely Cut	
	(n=6)		(n=5)		(n=5)	
	Pre stim	Post stim	Pre stim	Post stim	Pre stim	Post stim
HR, beats/min	121.3 (7.6)	127.5 (25.6)	128.0 (6.7)	124.8 (10.3)	122.2 (14.7)	134.2 (12.8)
BPS, mm Hg	103.7 (21.5)	116.7 (45.6)	107.2 (24.1)	107.0 (31.9)	109.0 (28.2)	121.3 (21.4)
BPD, mm Hg	58.2 (18.4)	66.7 (28.7)	63.8 (17.3)	66.2 (26.1)	70.0 (18.2)	79.3 (12.6)
AERP, ms	158.3 (19.4)	143.3 (24.2)	154.0 (19.5)	146.0 (26.1)	150.0 (26.5)	155.0 (12.9)
VERP, ms	161.7 (13.3)	163.3 (29.4)	156.0 (11.4)	160.0 (18.7)	164.0 (19.5)	162.5 (20.6)
R-R interval, ms	502.8 (35.1)	484.7 (96.7)	466.6 (30.5)	488.6 (47.9)	496.8 (65.0)	441.8 (51.0)
PR interval, ms	119.3 (8.6)	103.3 (25.4)	115.0 (7.2)	116.4 (12.7)	127.2 (8.3)	113.8 (10.0)
QRS, ms	61.2 (6.3)	58.5 (5.0)	62.6 (5.4)	61.2 (6.4)	59.2 (5.1)	59.3 (6.5)
QT interval, ms	263 (27.0)	246.3 (29.2)	248.6 (9.6)	242.2 (24.5)	254.6 (30.0)	238.0 (13.4)

LA conduction, ms	25.2 (10.9)	22.3 (10.3)	29.0 (10.9)	28.0 (8.5)	26.4 (11.3)	28.3 (12.3)
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Abbreviations: AERP, atrial effective refractory period; BPD, diastolic blood pressure; BPS, systolic blood pressure; HR, heart rate; LA, left atrial; LV, left ventricular; SG, stellate ganglion; stim, stimulation; VERP, ventricular effective refractory period.

^a All values are mean (SD).





