Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia

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BACKGROUND The sympathetic nervous system is thought to play a role in the genesis of ventricular tachyarrhythmias (VT). Left and added right cardiac sympathectomy have been shown to reduce the burden of arrhythmias in the setting of a VT storm. However, the contribution of the right stellate ganglion (RSG) and the left stellate ganglion (LSG) to the innervation of the anterior left ventricular (LV) wall is not well understood.

OBJECTIVE To evaluate the innervation of the anterior LV wall by the LSG and the RSG.

METHODS The heart and stellate ganglia were exposed via sternotomy in pigs with normal hearts (n = 8). A 20-electrode catheter was placed on the anterior LV wall to record activation recovery interval (ARI), a surrogate measure of action potential duration. A microdialysis catheter was inserted in a similar location to sample interstitial norepinephrine (NE) content. ARI and NE measurements were recorded at baseline and during LSG and RSG stimulation.

RESULTS LSG stimulation shortened ARI by 17.1% ± 10.5% (mean ± standard error), while RSG stimulation shortened ARI by 42.1% ± 15.7%, $P = .04$ (LSG vs RSG). LSG stimulation increased interstitial NE levels by 200% ± 65%, while RSG stimulation increased the NE content by 260% ± 40% ($P = .012$). LSG stimulation increased dispersion in ARI from 376.0 ± 83.7 ms^2 to 1242.5 ± 566 ms^2 ($P = .03$) and caused ventricular fibrillation in 2 pigs. During RSG stimulation, dispersion increased from 419 ± 65.8 to 474.8 ± 81 ms^2 ($P = .4$).

CONCLUSIONS Both the LSG and the RSG provide significant innervation to the anterior LV wall as demonstrated by both ARI shortening and NE concentrations. LSG stimulation significantly increases ARI dispersion. This study provides mechanistic insight into the beneficial effects of left sympathectomy and the additional role of right sympathectomy in reducing arrhythmias in patients with anterior myocardial scars and VT storm.

KEYWORDS Cardiac sympathetic innervation; Ventricular arrhythmias

ABBREVIATIONS ARI = activation recovery interval; **EGM** = electrogram; **LSG** = left stellate ganglion; **LV** = left ventricular; **NE** = norepinephrine; **RSG** = right stellate ganglion; **VF** = ventricular fibrillation; **VT** = ventricular tachyarrhythmia

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Introduction

The sympathetic nervous system plays an important role in the genesis and maintenance of ventricular arrhythmias.[1,2] Blockade of direct sympathetic stimulation via beta blockers reduces the risk of sudden cardiac death.[3] Left cervicothoracic sympathectomy reduces ventricular tachyarrhythmia/ventricular fibrillation (VT/VF) episodes in dog models of myocardial infarction and in humans with myocardial infarction.[4,5] Furthermore, thoracic epidural anesthesia and left cervicothoracic sympathectomy have been advocated to decrease the burden of VT in patients with myocardial infarction, cardiomyopathy, and refractory ventricular tachycardia.[6,7] Recently, bilateral cervicothoracic sympathectomy, with removal of both the right stellate ganglion (RSG) and the left stellate ganglion (LSG), has also been shown to control refractory VT in a small number of patients with ischemic or nonischemic cardiomyopathy.[8] The mechanism behind these beneficial effects is not well understood.

The innervation of the left ventricle by the RSG vs the LSG, even in the setting of a normal heart, is controversial. Previous studies in canine models have shown predominantly RSG innervation of the anterior ventricles, while LSG predominated on the posterior aspect of the right and left ventricles.[9] Opthof et al by studying VF intervals during stimulation found significant interanimal variability but concluded that the LSG did not significantly innervate the anterior left ventricular (LV) wall.[10] However, other studies have shown either no change in the ventricular refractory period of the anterior LV wall with RSG stimulation or a paradoxical decrease in the ventricular refractory period

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with RSG removal.[11–13] The aim of this study was to assess the innervation of the anterior LV wall by the RSG vs LSG in porcine hearts, using both electrophysiological and biochemical techniques to provide a comprehensive assessment of functional changes during stellate ganglia stimulation. We hypothesized that both RSG and LSG innervate the anterior LV wall. Furthermore, given the effects of left stellectomy in animal models and patients with myocardial infarction, we postulated that LSG stimulation is more proarrhythmic by creating a greater effect on the dispersion of repolarization.

Methods

Surgical preparation

Animal handling and care followed the recommendations of the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the University of California, Los Angeles, Institutional Animal Care and Use Committee. Animal protocols were approved by the University of California, Los Angeles, Chancellor's Animal Research Committee.

Female Yorkshire pigs (n = 8) weighing 25–40 kg were medicated with intramuscular telazol (8–10 mg/kg) and fentanyl (50–100 μg) and then intubated and ventilated. General anesthesia was maintained with inhaled isoflurane (0.8%–1.5%) and intermittent timed boluses of fentanyl to maintain analgesia. Animals underwent median sternotomy and bilateral thoracotomy to expose the anterior surface of the heart and sympathetic nerves of the posterior thorax. Continuous intravenous saline was infused throughout the procedure, and anesthesia and hemodynamics were monitored closely during experimental protocols by using a surface electrocardiogram and radial arterial line. Animals were euthanized by intravenous administration of a lethal dose of potassium chloride and sodium pentobarbital (100 mg/kg).

Stellate ganglion stimulation

Exposed LSG and RSG were electrically stimulated for 10 minutes by using a platinum bipolar electrode connected to a Grass stimulator (S9D; Grass Technologies, West Warwick, RI). Stellate stimulation consisted of repeated square wave pulses (5- ms duration) delivered at 5 Hz with stimulus amplitude of 10 V similar to prior studies.[14–16] Animals were randomly assigned to first receive LSG and then RSG stimulation, or vice versa, with a 60-minute interval between stimulations.

Hemodynamic recordings

Systolic LV pressures were assessed by using a 5-F pigtail, 12-pole conductance-pressure catheter connected to an MPVS Ultra processor (Millar Instruments, Inc, Houston, TX) placed in the left ventricle via carotid artery sheath under ultrasound guidance. Proper catheter position was confirmed by the examination of segmental volume signals. Pressure was continuously monitored and recorded throughout experiments. Increases in LV pressures were noted at stimulation onset, confirming successful stimulation capture. Furthermore, a femoral arterial catheter was also placed and used for systemic arterial pressure monitoring. Electrocardiogram was continuously recorded.

Norepinephrine analysis via microdialysis

Norepinephrine (NE) was collected from the interstitial fluid by using a microdialysis catheter (diameter of 0.5 mm, membrane length 4 mm; CMA 20, CMA Microdialysis, Solna, Sweden) placed on the anterior surface of the left ventricle to the left of the left ascending artery. The microdialysis probe was implanted by using a steel guiding needle and split plastic tubing. The dialysis probe was perfused with Lactated Ringer's solution at 2.0 μL/min with a CMA/100 microinjection pump. After placement of the microdialysis catheter, a period of 120 minutes was allowed to elapse before any collection was performed. This stabilization period was introduced so that any interstitial NE release from injury would subside, as confirmed in previous studies, and steady-state levels could be reached.[17–20] Dialysate volumes of 20 μL were collected in microvials containing 20 μL of a solution of 2% Ethylenediaminetetraacetic acid (EDTA) in 0.08 N acetic acid. Sampling time was two 5-minute intervals for a total of 10 minutes during LSG and RSG stimulation and 5 minutes at baseline in order to collect sufficient amounts of interstitial NE for analysis. The recovery rate of the microdialysis probe was approximately 25%, which was checked in vitro before each experiment. At the end of each experiment, the implant site was checked to confirm that the dialysis probe had been correctly implanted in the LV myocardium. Interstitial fluid was collected by using a CMA pump and stored at $\tilde{8}0$°C until analysis was performed. To ensure that the hemodynamic response seen with stellate stimulation was not due to circulating catecholamines, peripheral arterial, venous, and coronary sinus NE was also collected prior to and during stimulation of the ganglia. Coronary sinus NE was collected during coronary sinus occlusion with a balloon-tipped catheter.

NE level analysis in blood as well as the interstitial fluid was performed by using an ultrasensitive enzyme immune-linked assay (ELISA 5200) with a sensitivity of 1.5 pg/sample (Rocky Mountain Diagnostics, CO), and an ELISA microplate reader (Fisher Scientific, Waltham, MA) was used to quantify the results. Blood samples were initially centrifuged (1500*g*, 15 minutes) to separate the plasma portion prior to performing ELISA.

Activation recovery interval recordings

Local action potential duration (APD) was measured by using the activation recovery interval (ARI) method.[16–18] In brief, ARI is measured as the time between maximum negative dV/dt of the activation signal to the maximum positive dV/dt of the repolarization wave in the local electrogram (EGM). This method has been previously validated in multiple studies as an excellent surrogate of local APD_{90} and has the advantage of allowing simultaneous recording of

multiple regions by using standard multipolar pacing catheters.[21–23]

For ARI analysis, a multipolar catheter (20 electrodes, 2-mm spacing, St Jude Medical, St Paul, MN) was lightly sutured on the anterior LV surface to the left of the LAD. Baseline EGM recordings from all electrodes were obtained prior to LSG and RSG stimulation (filter setting 0.05–500 Hz) and during stimulation by using a dedicated animal PruckaCardiolab EP system (GE Healthcare, Waukesha, WI). Epicardial unipolar EGMs were obtained from the multipolar catheter, and ARI was analyzed by using customized software, Scaldyn M (University of Utah, Salt Lake, UT). Examples of ARIs obtained at baseline and during stimulation are shown in Figure 1. A minimum of 30 EGMs were analyzed from each electrode just prior to and at peak stimulation, which usually occurred at 3–5 minutes postinitiation of stimulation.

Statistical analysis

For comparison of continuous variables, the Wilcoxon rank sum test was used. For ARI analysis, a mixed repeated-measures analysis of variance was used to compare the mean ARI and adjusted mean change in ARI from baseline. The change in ARI and NE concentration was used for analysis to adjust for any baseline differences that are due maybe to minute-to-minute variation in the autonomic state of the animal. For the analysis of ARI dispersion, the variance in ARI comparing baseline to stimulation was assessed by using the Bartlett test. The hemodynamic and interstitial NE measurements were compared in the experimental stages by repeated-measures analysis of variance followed by the post hoc Bonferroni correction. Data are presented as mean ± standard error unless noted otherwise. SAS 9.1 was used for statistical analysis. A P value of .05 or less was considered significant.

Results

Hemodynamic response

Peak hemodynamic response to LSG and RSG stimulation was seen at approximately 4.29 ± 2.02 and 2.43 ± 0.53 minutes (mean ± standard error), respectively (P = .039). LSG stimulation increased the heart rate from 79.4 ± 4.7 to 91.1 ± 7.6 beats/min and blood pressure from 61.7 ± 6.9 to 79.1 ± 12.5 mmHg at peak stimulation. RSG stimulation increased the heart rate from 86.7 ± 5.2 to 148.3 ± 10.4 beats/min and blood pressure from 57.9 ± 4.6 to 78.7 ± 8.6 mmHg (Figure 2). RSG stimulation had a significantly greater effect than LSG stimulation on heart rate (P <.01).

Interstitial NE analysis

Prior to LSG stimulation, the baseline interstitial NE levels were 0.6 ± 0.2 ng/mL (mean ± standard error). The interstitial NE levels increased to 1.26 ± 0.7 ng/mL with LSG stimulation, an increase of 200% ± 65%. Interstitial NE levels prior to RSG stimulation were 0.49 ± 0.2 ng/mL and increased to 1.29 ± 0.5 ng/mL on the anterior wall with RSG stimulation, an increase of 260% ± 40% (Figure 3). Therefore, although both LSG and RSG increased interstitial NE levels, RSG increased interstitial NE levels significantly more than did LSG (P = .012).

ARI analysis

LSG stimulation decreased ARI by a mean of 72 ± 17 ms from a baseline value of 419 ± 32 ms. RSG stimulation

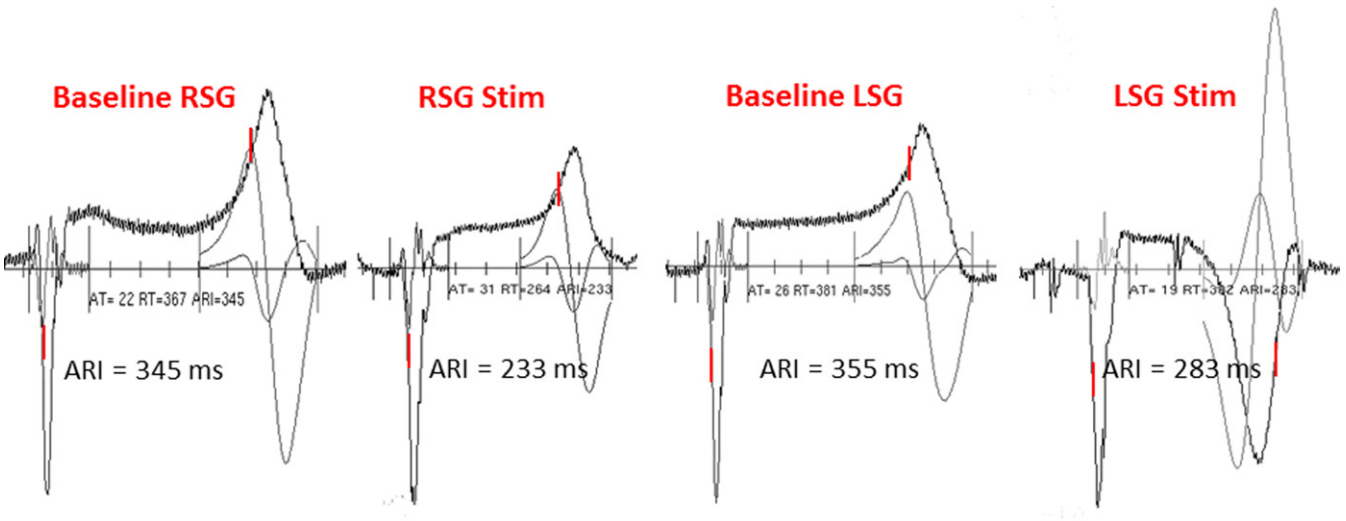

Figure 1 EGM recordings and calculation of ARI. Examples of the baseline EGMs prior to LSG and RSG stimulation are shown for a single electrode. The EGMs during LSG and RSG stimulation for the same electrode are also shown. ARI decreases from baseline during both LSG and RSG stimulation in this electrode on the anterior left ventricular wall. The gray curves represent the derivative curves obtained by Scaldyn, and the red lines are placed at points along the EGM representing the most negative dV/dt of the activation wave front and the most positive dV/dt of the repolarization wave front. ARI represents the time between the 2 red marks, as calculated by Scaldyn. Scale = 50 ms per hash mark. ARI = activation recovery interval; = electrogram; AT = activation time; LSG Stim = during left stellate ganglion stimulation; RSG Stim = during right stellate ganglion stimulation; RT = repolarization time.

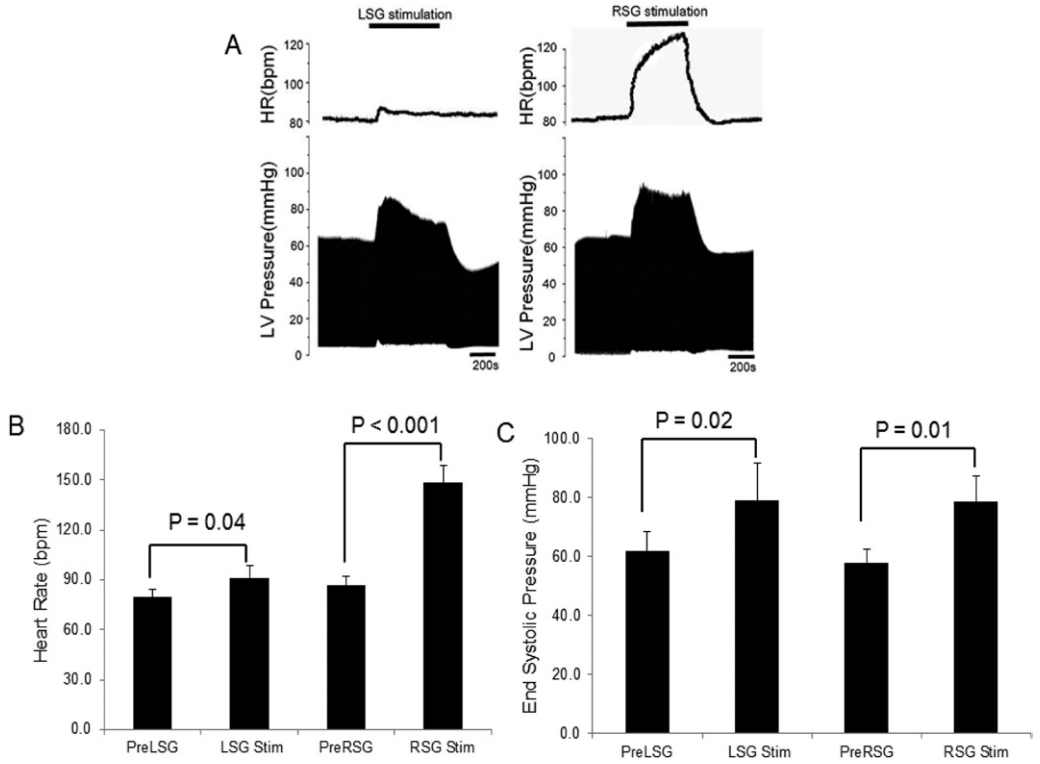

Figure 2 Hemodynamic response to LSG and RSG stimulation. RSG causes a greater rise in heart rate than stimulation LSG (panels A and B), while LSG and RSG stimulation both cause increases in end systolic pressure that were not significantly different (panels A and C). HR = heart rate; LAD = left ascending artery; LSG Stim = during left stellate ganglion stimulation; LV = left ventricular; RSG Stim = during right stellate ganglion stimulation.

decreased ARI by a mean of 146 ± 29 ms from a baseline value of 350 ± 28 ms on the anterior wall. Therefore, the mean percentage change in ARI with LSG stimulation was 17.1% ± 10% (mean ± standard error), while the percentage change in ARI with RSG stimulation was 42.1% ± 17.1% (P = .04; Figure 4).

The variance at baseline and during stimulation across the 20 electrodes on the anterior LV wall was calculated in each animal to assess the increase in ARI dispersion with stellate stimulation. The mean variance at baseline just prior to LSG stimulation was 376.0 ± 83.7 ms^2. The variance increased to 1242.5 ± 566 ms^2 at peak stimulation. Two of the 8 pigs went into VF at peak LSG stimulation. The variance in ARI prior to RSG stimulation was 419 ± 65.8 ms^2. During peak RSG stimulation, the variance increased to 474.8 ± 81 ms^2. None of the pigs in this series developed

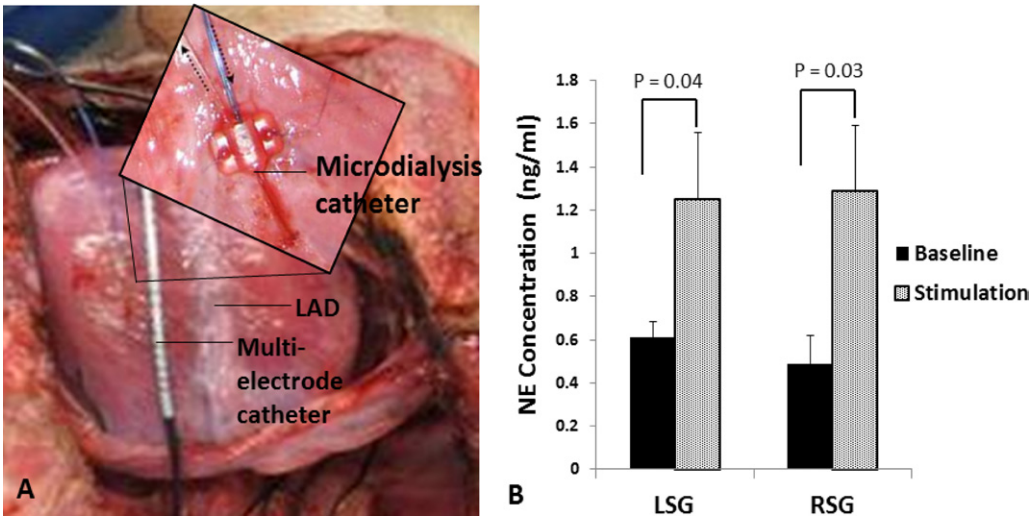

Figure 3 Experimental setup. The location of the microdialysis and multielectrode catheter on the anterior LV wall (panel A). The concentration of NE before and after LSG and RSG stimulation (panel B). NE levels increase with both LSG and RSG stimulation in the anterior wall. LSG = left stellate ganglion; NE = norepinephrine; RSG = right stellate ganglion.

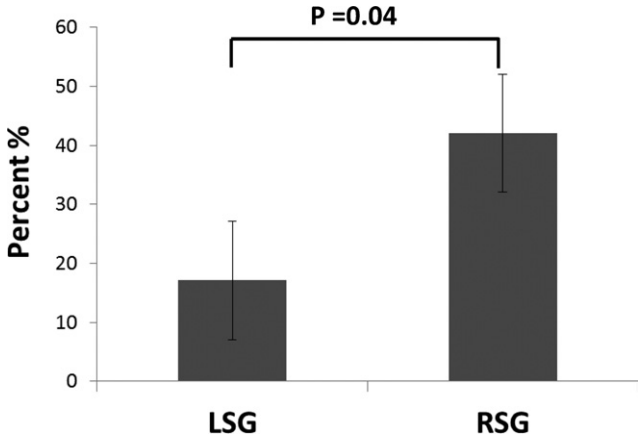

Figure 4 ARI response to LSG and RSG stimulation. The change in ARI with LSG and RSG stimulation is demonstrated. A decrease in ARI is seen with both LSG and RSG stimulation from baseline, although RSG stimulation decreases ARI more than does LSG stimulation on the anterior wall. ARI = activation recovery interval; LSG = left stellate ganglion; RSG = right stellate ganglion.

VF with RSG stimulation. Thus, LSG stimulation increased dispersion in ARI by 65% ± 32% (P = .03), while there was no significant increase in dispersion with RSG stimulation across the electrodes on the anterior wall (P = .4; Figure 5). Of note, in the 2 pigs that developed VF, LSG increased the dispersion in ARI, just prior to fibrillation, by 285%. Initiation of VF in one of these animals is shown in Figure 6.

Discussion

Major findings

This study demonstrates that in the porcine heart (1) the functional innervation of the anterior LV wall is shared by LSG and RSG, and (2) LSG stimulation significantly increases the dispersion in repolarization of the anterior LV wall.

Innervation of the anterior LV wall

Innervation of the anterior LV wall remains unclear, if not controversial. In 1966, Yanowitz et al[9] showed that right stellectomy increased the ventricular refractory period on the anterior wall while left stellate sympathectomy had a greater effect on the posterior wall. However, this study was limited by the small number of electrodes and the great variability in refractory periods observed across the anterior and posterior walls of the ventricles. Furthermore, the ventricular refractory periods were measured only during blockade, not stimulation of the stellate ganglia. Millar et al[21] in 1975 showed that recurrent cardiac nerve stimulation (a branch of the RSG) produced marked shortening of the refractory period of the interventricular septum with lesser changes seen on the anterior wall. However, a branch of the LSG, the ventromedial cardiac nerve, also produced changes in effective refractory period on the septum and anterior wall, suggesting innervation of the anterior wall by both stellate ganglia, with the right stellate predominating.[24] On the other hand, Opthof et al[25] while studying VF intervals in an arrested canine heart during sympathetic stimulation concluded that the LSG primarily innervated the posterior wall while the RSG primarily innervated the anterior wall. Haws and Burgess[26] suggested that at sites of overlapping innervation, LSG stimulation shortened ventricular refractory periods more than did RSG stimulation. And in 1992, Garcia-Calvo et al did not observe significant shortening of the LV refractory period with RSG stimulation in an open chest dog model.[13] In patients with structurally normal hearts who presented with supraventricular tachycardia, percutaneous RSG blockade did not lead to changes in the refractory period of the ventricles.[12]

Given the above controversy, in this study, we employed dual electrophysiological and biochemical techniques to provide a more comprehensive assessment of functional changes during stellate ganglia stimulation: (1) multielectrode recordings, which allowed measurement of ARI at 20 sites across the anterior LV wall, and (2) microdialysis for quantification of interstitial NE release from sympathetic nerve endings. LSG stimulation decreased ARI by 17.1% ± 10.5% (mean ± standard error), while RSG stimulation shortened ARI by 42.1% ± 15.7%. LSG stimulation increased interstitial NE levels by 200% ± 65%, while RSG increased NE content by 260% ± 40%. Thus, both the LSG and the RSG provide significant innervation to the anterior LV wall.

Stimulation of the stellate ganglia and proarrhythmia

Previous studies have suggested that LSG stimulation may be more proarrhythmic than RSG stimulation. But few data exists on the mechanism leading to proarrhythmia. In 1988, Ben-David and Zipes[27] observed a greater increase in the amplitude of early afterdepolarization with LSG stimulation than with RSG stimulation. Priori et al[28] showed that left stellate stimulation caused delayed afterdepolarizations in vivo in cat hearts, suggesting triggered activity as the mech-

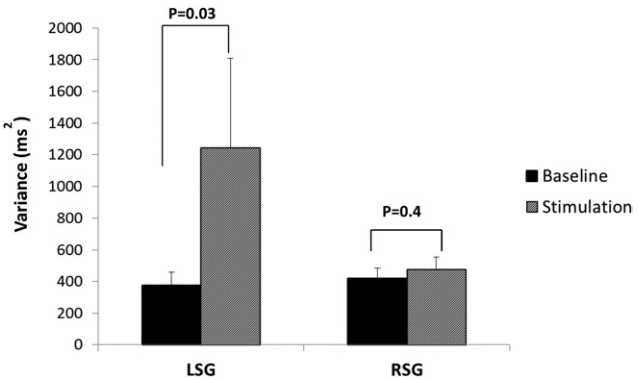

Figure 5 Dispersion in ARI LSG vs RSG stimulation on the anterior wall. The dispersion in ARI, measured as the mean variance across the electrodes in each porcine heart, before and after LSG and RSG stimulation is shown. LSG stimulation increases dispersion significantly more than does RSG stimulation. ARI = activation recovery interval; LSG = left stellate ganglion; RSG = right stellate ganglion.

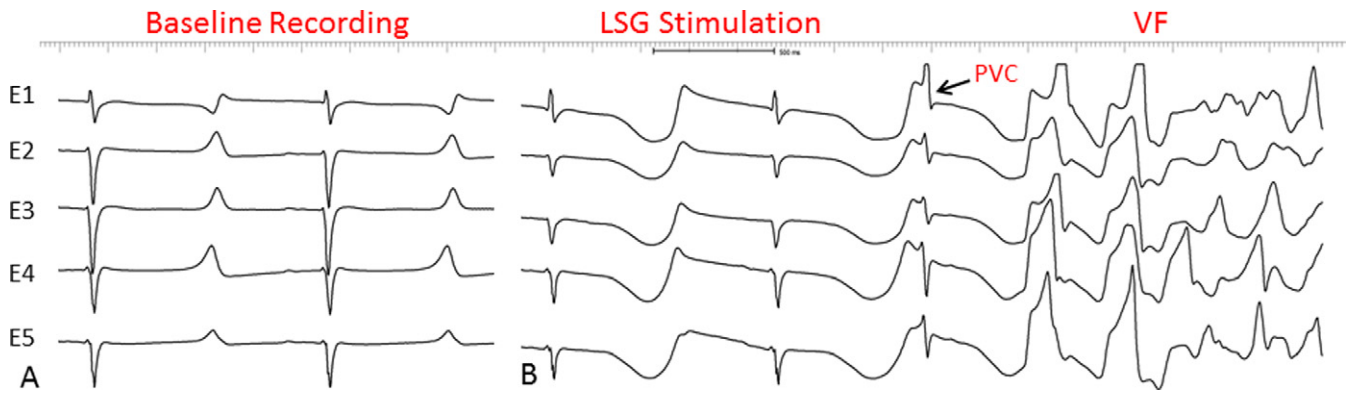

Figure 6 Initiation of VF during LSG stimulation. The baseline electrograms from 5 electrodes are shown in the left panel **(A),** and the effect of LSG stimulation and the initiation of VF is shown in the right panel **(B)**. VF is initiated by a premature ventricular contraction (PVC) (arrow). LSG = left stellate ganglion; VF = ventricle fibrillation.

anism of ventricular arrhythmogenesis. Opthof et al[25,29,30] noted an increase in dispersion with sympathetic stimulation during cardiac arrest with the heart in VF both during ischemia and in normal canine hearts although this study showed a great deal of interanimal variability and was limited by the fact that the hearts had to be arrested and placed in VF in order to assess repolarization intervals. Janse et al[31] showed greater conduction during ischemia in canine hearts in the ischemic zone with LSG stimulation, and Gantenberg and Hageman[32] showed increased incidence of VF in canine hearts with LSG stimulation but not with RSG stimulation. These studies have provided support to the value of stellectomy in the prevention of VT. For instance, in conscious dogs with prior anterior myocardial infarction, left stellectomy seemed to protect against VF during acute myocardial ischemia.[33] In an anesthetized dog model without prior MI, either left or right stellectomy protected against death by VF after coronary occlusion.[34] Furthermore, left cervicothoracic sympathectomy has been shown to decrease the burden of ventricular arrhythmias in cardiomyopathy patients presenting with electrical storm.[6] In this study, LSG stimulation significantly increased dispersion in ARI across the anterior LV wall by 65% ± 32% and caused VF in 2 normal porcine hearts. RSG stimulation, on the other hand, did not have a significant effect on dispersion. Therefore, this study further strengthens the association between adrenergic activation and ventricular arrhythmogenesis and suggests that reentry, due to significant differences in the ventricular refractory period, also serves as a mechanism.

Limitations

This study was limited to addressing the question regarding the contribution of RSG vs LSG in providing sympathetic innervation to the anterior LV wall. This is a clinically relevant question since right/bilateral stellectomy is being advocated as adjunctive treatment for patients with intractable VTs and many such patients have anterior LV scars. Furthermore, the effect of the heart rate on ARI, which was greater with RSG as compared with LSG was not readily correctable. For this reason, NE analysis was also performed to confirm ARI findings.

Isofluorane can suppress sympathetic nerve activity. Although in this study, robust hemodynamic response was seen during LSG and RSG stimulation, it is possible that our results are a more conservative estimate of the true effects of sympathetic stimulation on the anterior LV wall.

Conclusions

This study demonstrates that the innervation of the anterior LV wall is shared by the RSG and the LSG. In this in vivo porcine model with intact cardiac autonomic innervation, RSG decreases ARI more than does LSG, while LSG stimulation significantly increases dispersion in the refractory period across the normal ventricular wall. This study further strengthens the link between ventricular arrhythmias and sympathetic innervation and provides insights into the mechanism behind the beneficial effects of sympathectomy in reducing arrhythmias in patients with anterior myocardial scars and VT storm.

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