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Modulation of regional dispersion of repolarization and T-peak to T-end interval by the right and left stellate ganglia

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Vaseghi M, Yamakawa K, Sinha A, So EL, Zhou W, Ajijola OA, Lux RL, Laks M, Shivkumar K, Mahajan A. Modulation of regional dispersion of repolarization and T-peak to T-end interval by the right and left stellate ganglia. Am J Physiol Heart Circ Physiol 305: H1020–H1030, 2013.—Left stellate and right stellate ganglion stimulation (LSG and RSG, respectively) are associated with ventricular tachyarrhythmias; however, the electrophysiological mechanisms remain unclear. We assessed 1) regional dispersion of myocardial repolarization during LSG and RSG and 2) regional electrophysiological mechanisms underlying T-wave changes, including T-peak to T-end (Tp-e) interval, which are associated with ventricular tachyarrhythmia/ventricular fibrillation. In 10 pigs, a 56-electrode sock was placed around the heart, and both stellate ganglia were exposed. Unipolar electrograms, to assess activation recovery interval (ARI) and repolarization time (RT), and 12-lead ECG were recorded before and after LSG and RSG. Both LSG and RSG increased dispersion of repolarization; with LSG, the greatest regional dispersion occurred on the left ventricular (LV) anterior wall and LV apex, whereas with RSG, the greatest regional dispersion occurred on the right ventricular posterior wall. Baseline, LSG, and RSG dispersion correlated with Tp-e. The increase in RT dispersion, which was due to an increase in ARI dispersion, correlated with the increase in Tp-e intervals (R2 = 0.92 LSG; and R2 = 0.96 RSG). During LSGS, the ARIs and RTs on the lateral and posterior walls were shorter than the anterior LV wall (P < 0.01) and on the apex versus base (P < 0.05), explaining the T-wave vector shift posteriorly/inferiorly. RSGS caused greater ARI and RT shortening on anterior versus lateral or posterior walls (P < 0.01) and on base versus apex (P < 0.05), explaining the T-wave vector shift anteriorly/superiorly. LSGS and RSGS cause differential effects on regional myocardial repolarization, explaining the ECG T-wave morphology. Sympathetic stimulation, in line with its proarrhythmic effects, increases Tp-e interval, which correlates with increases in myocardial dispersion of repolarization.

sympathetic nervous system; ventricular tachyarrhythmias; myocardial repolarization

SUDDEN CARDIAC DEATH (SCD), predominantly due to ventricular tachyarrhythmias [ventricular tachyarrhythmia (VT)/ventricular fibrillation (VF)], causes more than 300,000 deaths in the United States (47). The autonomic nervous system plays an important role in the genesis of VTs (37, 46), with neuromodulation emerging as an innovative therapeutic approach in the management of these arrhythmias (1, 4, 7, 33, 34). Left stellate ganglion (LSG) stimulation is known to be arrhythmogenic, with associated increases in early afterdepolarizations, delayed afterdepolarizations, overall myocardial dispersion of repolarization, and incidence of VF at baseline and during ischemia (3, 15, 24, 26, 27, 29). The role of the right stellate ganglion (RSG) has been less clear, with observed variability regarding arrhythmias and dispersion (15, 19, 27, 30). Bilateral stellate ganglion stimulation has been associated with reversal in direction of ventricular repolarization (18). Recent success of bilateral stellate ganglionectomy suggests that RSG may also contribute to arrhythmogenesis (1). Given the essential role of sympathetic neural innervation in modulating VTs, it is important to comprehensively assess the electrophysiological mechanisms whereby RSG and LSG exert control over regional ventricular repolarization and dispersion. Prior studies, while providing important insight into the role of RSG and LSG, were limited by ventricular refractory periods derived from pacing or derived indirectly from VF intervals, both techniques that can alter autonomic tone (13).

Further understanding of the sympathetic neural control in arrhythmogenesis is aided by defining the relationship between regional myocardial dispersion during LSG and RSG stimulation and changes in electrocardiographic (ECG) indexes of repolarization (T-wave morphology and vectors), which are associated with SCD. In porcine hearts, LSG stimulation shifts the T-wave vector to a posterior and inferior axis, whereas RSG stimulation shifts the T-wave vector anteriorly and superiorly (31). The mechanisms behind the T-wave changes during adrenergic stimulation are not well understood and can be potentially gleaned from regional myocardial repolarization differences. Additionally, T-peak to T-end (Tp-e) interval has been found to be an independent risk factor for SCD (28), and prolongation in Tp-e interval was seen in a canine infarct model before VT (44); yet the effects of LSG and RSG stimulation on this interval remain to be established.

The purpose of this study was 1) to assess changes in regional myocardial repolarization and dispersion of repolarization that are associated with VT/VF during LSG and RSG stimulation and 2) to evaluate the relationship of changes in regional activation recovery interval (ARI) and repolarization time (RT), global ARI and ARI, and RT dispersion with T-wave morphology and Tp-e, which has been associated with ventricular arrhythmias.
METHODS

Surgical preparation. Animal handling and care followed the recommendations of the National Institutes of Health’s 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 = 10) weighing 25 to 40 kg were medicated with intramuscular telazol (8–10 mg/kg) and fentanyl (50–100 μg), and then intubated and ventilated to maintain arterial partial pressure of CO₂ at 38–42 mmHg. General anesthesia was maintained with inhaled isoflurane (1.2–1.5%) and intermittent 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 to maintain euvoeemia. At the end of the procedure, the animals were euthanized by intravenous administration of a lethal dose of sodium pentobarbital (100 mg/kg).

Stellate ganglia stimulation. Exposed LSG and RSG were electrically stimulated for 5 min, each using a platinum bipolar electrode connected to a Grass S88 dual-output stimulator (Grass Technologies, West Warwick, RI). Stellate stimulation consisted of repeated square wave pulses of 5-ms duration, delivered at 5 Hz, with stimulus amplitude of 4–10 V similar to prior studies (20, 21, 31). Animals were randomly assigned to receive LSG and then RSG stimulation or vice versa, with a 30-min interval between stimulations.

Hemodynamic recordings. Left ventricular (LV) pressures were continuously recorded using a 5-Fr pigtail, 12- pole conductance-pressure catheter connected to a MPVS Ultra processor (Millar Instruments, Houston, TX) placed in the LV via carotid artery sheath under ultrasound guidance. Proper catheter position was confirmed by cardiac ultrasound and by examination of appropriate segmental volume signals. Increases in LV pressures were noted at stimulation onset, confirming successful stimulation. Continuous systolic blood pressure (SBP) via femoral arterial line was measured.

Surface ECG recordings. Continuous 12-lead ECG data were recorded using a holter monitoring system (H12+ digital monitor; Mortara Instruments, Milwaukee, WI). Frontal plane lead electrodes were placed in standard positions. To accommodate the open-chest surgical procedure, precordial lead electrodes V1 through V6 were placed posteriorly in the positions of V6 through V11 to mirror standard, anterior, precordial lead electrode placement and record the horizontal plane. ECGs were analyzed manually. T-wave vector changes in the ventral-dorsal (horizontal plane) and superior-inferior (frontal plane) were assessed using posteriorly placed leads as well as limb leads. Time from peak to end of T-wave (Tp-e) was measured from maximal T-wave voltage to the end of T-wave in limb leads with the clearest T-wave recording.

Plasma norepinephrine analysis. To ensure that the hemodynamic response seen with stellate stimulation was not due to alterations in circulating catecholamines, peripheral arterial, venous, and coronary sinus norepinephrine (NE) were collected before and during stimulation of the stellate ganglia. Coronary sinus NE was collected during occlusion with a balloon tipped catheter. Although coronary sinus NE levels may not directly reflect ventricular interstitial release of NE (as they may more likely reflect NE released from the coronary sinus musculature), they provide a surrogate for adequate LSG and RSG stimulation. (10) Measurement of NE concentration was performed using an ultrasensitive enzyme immune-linked assay (ELISA 5200) with a sensitivity of 1.5 pg/sample (Rocky Mountain Diagnostics), and an ELISA microplate reader (Fisher Scientific, Waltham, MA) was used to quantify the results. Blood samples were initially centrifuged (1500 g, 15 min) to separate the plasma portion before performing ELISA.

ARI recordings. Local epicardial action potential duration (APD) was measured using the ARI method. ARI has been corroborated to be a reliable a surrogate for APD by use of simultaneously acquired intracelular recordings and monophasic APD recordings and has been validated in both animal models and humans (6, 12, 16, 22, 40, 43). Briefly, in each electrogram, activation time was measured as the time of minimum first derivative of voltage (dV/dt) in the depolarization wave—the intrinsic deflection—and RT is measured as the time of maximum dV/dt near the peak of the repolarization wave (T wave); the difference, ARI, reflects APD at the electrode site. The moment of maximum dV/dt has been shown to correspond well to local repolarization (8). This method also has the advantage of allowing for simultaneous repolarization measurements in the heart. In addition, for the purposes of this study, changes in ARI at a given site during an intervention correlate extremely well with changes in APD measured with microelectrodes (6, 12, 16, 22), and this method allows for measurement of local APD without pacing, extrastimulus delivery, or induction of VF that can alter autonomic tone. Repolarization time was defined as activation time plus ARI.

For activation time, ARI, and RT analysis, a 56-electrode, flexible, nylon sock was placed over the heart such that it surrounded the entire ventricular epicardium. Baseline electrogram recordings from all electrodes were obtained before LSG or RSG stimulation (filter setting, 0.05–500 Hz) and during stimulation using a dedicated animal Prucka Cardiolab EP system (GE Healthcare, Waukesha, WI). Epicardial, unipolar electrograms were obtained, and ARI was analyzed using customized software, Scaldyn M (University of Utah, Salt Lake, UT). A minimum of 15 electrograms were analyzed from each electrode just before and at peak stimulation. For the purposes of the article, anterior refers to the ventral aspect of the animal and posterior refers to the dorsal aspect of the animal. The heart was divided into eight segments: anterior LV, lateral LV, posterior LV, anterior right ventricular (RV), lateral RV, posterior RV, RV outflow tract or base and apex. In the porcine model, the epicardial apex is predominantly occupied by the LV. Effects of stimulation on ARI duration and variance on the anterior, lateral, posterior RV and LV, as well as base and apex were analyzed. The median number of electrodes in each region was 5 with a range of 4–7. Activation time, ARI, and RT polar maps were created using the Map3D (University of Utah) to better delineate ARI and RT changes during LSG and RSG stimulation.

Statistical analysis. For comparison of continuous variables, the paired Student’s t-test or Wilcoxon rank sum test was used. For regional analysis, means and variances in ARI and RT were compared using a parametric repeated-measure ANOVA model with type of stimulation (LSG/RSG), location, and their interaction as fixed effects and animal as a random effect. The change from baseline in NE concentration was used to assess adequacy of stellate stimulation. Global dispersion in ARI and RT was defined as the variance in the mean ARI recorded from all the electrodes over the entire ventricles. Regional dispersion in ARI was defined as the variance in the electrodes in a certain region. To account for baseline differences, the change in dispersion of repolarization and Tp-e interval was also compared and defined as the difference between stimulation and baseline value divided by the baseline value. Data are presented as means ± SE unless otherwise noted. SAS9.1 was used for statistical analysis. A P value of <0.05 was considered statistically significant.

RESULTS

Hemodynamic and NE response to stellate ganglion stimulation. Peak hemodynamic response to LSG and RSG stimulation was seen at ~1.3 ± 0.16 and 1.7 ± 0.14 mmHg, respectively. RSG stimulation increased heart rate from 71 ± 3 to 109 ± 5 beats/min, P < 0.05, systemic SBP from 77.5 ± 3.3 to 112 ± 4.7 mmHg, P < 0.05, and
maximum first derivative of LV pressure (dP/dt_{max}) from 974 ± 131 to 2,548 ± 362 mmHg/s, \( P < 0.05 \) at peak stimulation. LSG stimulation did not significantly affect heart rate (73 ± 4 to 75 ± 5 beats/min, \( P = 0.5 \)) but increased systemic SBP from 77.4 ± 3.4 to 100.9 ± 4.7 mmHg, \( P < 0.05 \), and LV dP/dt_{max} from 930 ± 156 to 2,084 ± 446 mmHg/s. RSG stimulation had a significantly greater effect on heart rate than LSG stimulation (\( P < 0.01 \), Fig. 1). Coronary sinus NE increased from 0.9 ± 0.3 ng/ml to 5.0 ± 1.4 ng/ml during RSG and from 0.9 ± 0.2 to 8.4 ± 5 ng/ml during LSG stimulation (\( P < 0.05 \) for LSG and RSG stimulation compared with baseline), with no significant changes in central arterial or inferior vena cava NE levels. When normalized for baseline, there was a 6.1 ± 3.3-fold increase in plasma NE levels with RSG stimulation compared with 8.3 ± 4.3-fold increase with LSG stimulation; however, this difference between RSG and LSG stimulation was not statistically significant (\( P = 0.3 \)).

**ECG changes during LSG and RSG stimulation.** Stimulation of the RSG and LSG increased Tp-e intervals. RSG stimulation prolonged Tp-e intervals on the surface ECG from 64 ± 2 to 73 ± 2 ms, \( P = 0.03 \). The difference in Tp-e intervals during stimulation compared with baseline was adjusted for heart rate using Bazett’s formula (from Tp-e 67 ± 2 at baseline to 98 ± 3 ms during stimulation, \( P < 0.01 \)). LSG stimulation also significantly prolonged Tp-e interval on the surface ECG from 68 ± 2 to 108 ± 5 ms, \( P < 0.001 \). When adjusted for the minimal change in heart rate, this prolongation remained significant (from 71 ± 2 to 112 ± 5 ms, \( P < 0.01 \), Fig. 2). LSG stimulation prolonged Tp-e interval more than RSG stimulation (\( P < 0.05 \), Fig. 2). In addition to increases in Tp-e, changes in the T-wave vector were also noted. At baseline, the T-wave vectors in both the horizontal (anterior-posterior direction) and frontal (superior-inferior direction) were variable. During RSG stimulation, the T-wave vector in all animals was

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**Fig. 1.** Hemodynamic response to left stellate ganglion (LSG) and right stellate ganglion (RSG) stimulation (LSGS and RSGS, respectively; top). Both RSGS and LSGS caused a significant rise in systolic blood pressure (SBP) and maximum first derivative of pressure (dP/dt_{max}), whereas only RSGS had a significant effect on heart rate (HR). Stim, stimulation; bpm, beats/min.
displaced anteriorly (ventrally) from 21.1 ± 19.1 to 106.7 ± 15° (Fig. 3) and superiority toward the RV from 73.1 ± 8.6 to 283.8 ± 5.7° (Fig. 4). LSG stimulation had the opposite effect. During LSG stimulation, the T-wave vector in all animals was displaced posteriorly (dorsally) from 15.5 ± 18 to 315.3 ± 8.5° in the horizontal plane and inferiorly from 78.1 ± 5.3 to 90.6 ± 5.3° in the frontal plane (Figs. 3 and 4).

Regional ARI and RT response to RSG and LSG stimulation. An example of the sock electrode configuration is shown in Fig. 5. There was no significant difference in the mean or standard deviation of the activation time during LSG stimulation compared with baseline (49 ± 3.5 vs. 48 ± 3.0 ms, P = not significant) and during RSG stimulation compared with baseline (53.3 ± 2.5 vs. 52.5 ± 3.0 ms, P = not significant). Furthermore, no significant regional differences in activation time were observed. At baseline, there was a significant difference in the mean ARI and RT of LV anterior wall compared with LV posterior wall (mean ARI of 487 ± 25 vs. 452 ± 27 ms and mean RT of 528 ± 26 vs. 504 ± 27 ms for RT, P < 0.05) but no statistically significant difference between the LV anterior wall and LV lateral wall (477 ± 25 ms for ARI and 528 ± 26 ms for RT, P = 0.1). The difference in RT was due to the difference in ARI. During LSG stimulation, the LV anterior wall mean ARI decreased to 460.9 ± 23 ms (RT = 510 ± 24 ms), the LV lateral wall ARI decreased to 414.6 ± 25 ms (RT = 465 ± 25 ms), and the LV posterior wall decreased to 383 ± 29 ms (RT = 434 ± 28 ms). Therefore, during LSG stimulation, the mean ARI and RT were shorter on the LV posterior wall, compared with LV anterior wall (P < 0.01) and LV lateral wall (P < 0.05). The regional ARI and RT of the RV followed the same pattern seen the on LV. Mean ARI decreased from 470 ± 27 to 464 ± 24 ms (P < 0.05) on the RV anterior wall, from 474.1 ± 26 to 456 ± 25.5 ms on the RV lateral wall, and from 468 ± 28 to 421 ± 32 ms (P < 0.05) on the RV posterior wall. The mean RT decreased from 524 ± 28 to 515 ± 24 ms on the anterior wall, from 528 ± 26 to 507 ± 26 ms on the RV lateral wall, and from 521 ± 30 to 472 ± 31 ms on the RV posterior wall. Therefore, the ARI and RT during LSG stimulation were shortest on the RV posterior wall compared with RV anterior wall (P < 0.01) and RV lateral wall (P < 0.05). Thus LSG stimulation greatly exacerbated any regional differences in repolarization that existed at baseline, exerting its greatest effects on the LV and RV posterior walls. These changes in regional RT explain the shift
of the T-wave vector posteriorly in the horizontal plane during LSG stimulation (Fig. 3).

We then compared basal to apical differences in RT and ARI at baseline and during LSG stimulation to see whether the shift in the ECG T-wave vector inferiorly during LSG stimulation could be explained. The mean ARI at baseline was 468.3 ± 19.6 ms and decreased to 447.9 ± 26.5 ms at the base; the mean ARI on the apex at baseline was 483 ± 16 ms and decreased to 402.6 ± 24.8 ms during LSG stimulation. The RT followed the same pattern as ARI. At the base of the heart, the mean RT was 523 ± 27 ms and decreased to 500 ± 26 ms. At the apex, the baseline RT was 537 ± 25 ms and decreased to 451 ± 24 ms during LSG stimulation. Therefore, during LSG stimulation, the difference in apicobasal ARI and RT was further accentuated, with the mean RT at the apex being much shorter than the base ($P < 0.05$), explaining the T-wave vector shift inferiorly (Fig. 4). The difference in apicobasal RTs was due to the difference in ARIs, as there were no significant changes in activation time.

During RSG stimulation, the mean ARI decreased from 491 ± 18 ms to 276 ± 26 ms and the mean RT decreased from 543 ± 16 to 320 ± 24 ms ($P < 0.01$) on the LV anterior wall. On the LV lateral wall, the mean ARI decreased from 470 ± 18 to 284 ± 29 ms and the mean RT from 541 ± 18 to 346 ± 27 ms ($P < 0.01$), and on the LV posterior wall, the mean ARI changed from 450 ± 16 to 305 ± 23 ms and the mean RT from 502 ± 15 to 359 ± 22 ms ($P < 0.01$). During RSG stimulation, there was a significant difference in the mean ARI and RT of the LV anterior wall versus posterior wall ($P < 0.01$) and LV lateral wall versus LV posterior wall ($P < 0.05$), with the LV anterior wall shortening more than LV lateral wall and with LV lateral wall shortening more than LV posterior wall. The regional mean ARI and RT of the RV reflected those of the LV, with the mean ARI and RT on the RV anterior wall shortening from 470.9 ± 21.3 to 270.3 ± 27.8 ms and from 522 ± 19 to 311 ± 24 ms, respectively ($P < 0.01$). On the RV lateral wall, the mean ARI decreased from 469 ± 21 to 271 ± 28 ms ($P < 0.01$), and the mean RT from 521 ± 19 to 326 ± 26 ms, $P < 0.01$. On the RV posterior wall, the mean ARI changed from 464 ± 20 to 295 ± 28 ms and the mean RT from 519 ± 21 to 346 ± 24 ms ($P < 0.01$). The shorter RT on the anterior walls of the heart compared with the posterior walls ($P < 0.01$ for RV anterior vs. RV posterior and $P < 0.05$ for RV lateral vs. RV posterior) can explain why the T-wave vector shifts anteriorly during RSG stimulation. The change in RT, however, is primarily driven by the change in ARI. We then investigated any apicobasal regional differences in mean ARI and RT during RSG stimulation. The base of the heart at baseline had a mean ARI of 468 ± 20 ms, which
decreased to 272 ± 28 ms (P < 0.01) with RSG stimulation and the apex of the heart had a mean ARI of 483 ± 16 ms, which decreased to 308 ± 29 ms during stimulation. Given no change in activation time, the RT changes followed the ARI changes and at the base of the heart decreased from 514 ± 17 to 318 ± 22 ms and at the apex decreased from 529 ± 13 to 354 ± 22 ms. Therefore, during RSG stimulation the RT at the base became shorter than the apex (P < 0.05) during RSG stimulation, explaining the T-wave vector shift superiorly (Fig. 4). An example of the activation, ARI, and RT polar maps for one animal is shown in Fig. 6. Regional analysis at baseline and during RSG and LSG stimulation shows that any regional differences in mean ARI and RT at baseline were exacerbated, and at times, completely reversed.

Global and regional dispersion in ARI in response to RSG and LSG stimulation. Given that there was no global or regional change in the mean activation time or variance of the activation time, the dispersion in ARI was identical to dispersion in RT. During LSG stimulation, the dispersion in epicar-
stimulation spontaneously caused VF in 4 of 10 animals. This ARIs (and RT) occurred in all 10 animals. Furthermore, LSG (and during RSGS and LSGS (Fig. 7).

Fig. 6. Activation time, ARI, and RT at baseline and in response to RSGS and LSGS. Polar maps of activation time (top), ARIs (middle), and RTs (bottom) generated from the sock electrode are shown at baseline (left), during RSGS (middle), and during LSGS (right) for one animal. RSGS demonstrates shorter ARIs and RTs on LV and RV anterior walls. However, during LSGS, ARIs and RTs on the posterior and lateral walls are shorter than other regions. No significant regional differences in activation time at baseline and during RSGS and LSGS, indicating that the predominant change responsible for differences in regional repolarization are due to ARI (local action potential duration) and not activation time.

dial repolarization increased from 534 ± 127 to 1,574 ± 198 ms² (P < 0.01). The increased dispersion in mean epicardial ARIs (and RT) occurred in all 10 animals. Furthermore, LSG stimulation spontaneously caused VF in 4 of 10 animals. This occurred without pacing or induction of VF and confirmed results from previous studies showing that LSG stimulation increases incidence of VF (5, 9). RSG stimulation increased epicardial dispersion of repolarization from 678 ± 70 to 958 ± 131 ms², P < 0.05. In eight porcine hearts, RSG stimulation increased dispersion, whereas in two hearts, overall epicardial dispersion decreased. RSG stimulation caused VF in one animal. The global epicardial dispersion of repolarization at baseline and during RSG and LSG stimulation correlated with Tp-e interval at baseline and during stimulation, (R² = 0.6, P < 0.01). The change in mean RT (and ARI) during LSG and RSG stimulation strongly correlated and linearly increased with the increase in Tp-e interval seen on the surface ECG (R² = 0.92, P < 0.01 for LSG stimulation, and R² = 0.96, P < 0.01 for RSG stimulation) (Fig. 7). This implies, particularly at baseline, though there may be other factors that modulate the Tp-e interval, that sympathetic stimulation increases the Tp-e interval by increasing dispersion in RT across the epicardial surface of the heart, linking Tp-e as a proarrhythmic ECG marker to the underlying myocardial mechanisms that explains the proarrhythmia.

There were no significant regional differences in dispersion in the LV or RV at baseline. Although the majority of regions increased their epicardial ARI with LSG stimulation, not all regions increased dispersion equivalently. LSG stimulation caused the greatest dispersion in ARI on the LV anterior wall and apex, which increased from 265. ± 25 to 2,381 ± 929 ms² (P = 0.028) and from 308 ± 62 to 2,390 ± 750 ms² (P = 0.014), respectively. The apical and anterior wall epicardial dispersion was significantly more than the RV anterior wall, RV lateral, RV posterior, RV outflow tract, and LV posterior wall (P < 0.05 for regional comparisons). However, RSG stimulation caused the greatest increase in dispersion on the RV posterior wall which increased from 450 ± 124 to 940 ± 198 ms² (P = 0.04). The dispersion on the RV posterior wall was greater than the LV posterior wall (P < 0.01), the LV lateral wall (P = 0.02), the RV lateral wall (P = 0.048), the RV anterior (P < 0.01), and apex (P = 0.02). Therefore, the greatest dispersion seems to occur in areas with the longest ARIs during RSG and LSG stimulation, suggesting that areas of overlapping innervation are most susceptible to increases in dispersion of repolarization during LSG and RSG stimulation (Fig. 8).
DISCUSSION

Major findings. The increase in dispersion of myocardial repolarization during sympathetic stimulation increases Tp-e interval. This is a novel finding of this study and potentially explains the mechanism underlying this pro-arrhythmic ECG marker of SCD.

LSG stimulation causes the greatest regional dispersion on the LV anterior wall and apex; RSG stimulation causes the greatest regional dispersion on the RV posterior wall. This is the first study to assess this important difference.

The greatest dispersion occurs in regions where each stellate ganglion has relatively sparse functional innervation. In this study, the greatest ARI dispersion during stimulation did not occur in the same regions as the greatest ARI shortening. Although areas of greatest ARI shortening were associated with increased dispersion, the most dispersion often occurred in regions with the longest mean ARI.

LSG stimulation causes the greatest shortening in ARI and RT on the lateral and posterior walls of both the RV and LV. Greater ARI and RT shortening was also noted at the apex, compared with the base of the heart following LSG stimulation; these findings are also novel to this study. These changes in RT mirrored and potentially explain the ECG T-wave vector changes, which shifted posteriorly and superiorly during LSG stimulation.

RSG stimulation, in contrast, causes the greatest shortening in ARI and RT on the anterior LV and RV epicardium. Furthermore, ARI and RT shortening occurred more at the base compared with the apex. These apicobasal changes have not been previously reported. These RT changes again mirrored the T-wave vector changes, which shifted anteriorly and superiorly (toward the RV base) during RSG stimulation.

RSG and LSG stimulation: epicardial RT and ARI dispersion and Tp-e interval. Tp-e interval is emerging as a new and robust marker of increased risk of SCD (28). In patients with acquired long QT syndrome, Yamaguchi et al. (41) showed that the Tp-e interval is more significant than QT dispersion or QTc in predicting Torsade de Pointes. An increase in Tp-e interval was found in LQT1 patients with exercise (36). Furthermore, in hypertrophic cardiomyopathy patients, Shimizu et al. (35) showed that Tp-e and not QTc predicted SCD. Prolonged Tp-e was associated with both inducible and spontaneous development of ventricular tachycardia in patients with history of VT and organic heart disease (39). It has been reported that Tp-e correlates with whole heart dispersion and not purely transmural dispersion (25). In this study, Tp-e interval at baseline and during stimulation correlated with dispersion in repolarization. The dispersion in RT was driven by dispersion in ARI as there was no change in the QRS or the activation time. This finding also confirms a previous study by Izumi et al. (14) that showed the Tp-e interval on the limb ECG leads reflects total spatial rather than transmural dispersion (14). Importantly, we have shown that the Tp-e interval increases with sympathetic stimulation, and this increase correlates strongly with the increase in epicardial dispersion of repolarization. When the QRS is constant, the Tp-e interval is a reflection of changes in phase 3 repolarization of the APD. The important effect of adrenergic stimulation on IKs during phase 3 of the APD potentially suggests the mechanism behind the strong link between Tp-e interval and dispersion of repolarization observed in this study. Therefore, this study provides insight into the link between adrenergic stimulation, proarrhythmia, and the reason behind the strong predictability of Tp-e interval as a surface EKG marker of SCD.

In this study, LSG stimulation increased dispersion in repolarization more than RSG stimulation, had a greater effect on Tp-e interval, and was more proarrhythmic, causing spontaneous VF in 40% of the animals. The increase in dispersion and arrhythmias associated with LSG stimulation during ischemia and normal canine and porcine hearts has also been previously reported (23, 24, 26, 27, 38). In open-chest dogs, electrical stimulation of LSG, left middle cervical, left caudal pole of the cardiopulmonary, or ventrolateral nerve caused VT in 13 of 22 normal dog hearts, with the isochronal mapping showing the earliest electrical excitation occurring on the posterior aspect of the ventricles (5). The likelihood for VT correlates with increasing coronary sinus NE levels (23). Electrical stimulation of the left ansae subclavia, LSG, and bilateral stellate ganglion stimulation increase incidence of ventricular arrhythmias during ischemia (9, 11). Furthermore, by measuring local VF intervals, Opthof et al. (26) showed that LSG stimulation can increase dispersion in refractoriness by shortening refractori-
ness across nonischemic sites while either not changing or increasing refractoriness at ischemic sites during coronary occlusion, increasing the dispersion across the ischemic border by 14–59%. On the other hand, left cervicothoracic sympatheticectomy in a canine model of myocardial infarction and in patients with ischemic and nonischemic cardiomyopathy has been shown to decrease burden of ventricular arrhythmias (4, 32, 34). Our findings are in line with the above studies showing that stellate ganglion stimulation increased global epicardial dispersion measured more than RSG stimulation.

Currently, it is unclear which patients benefit from left versus right cervicothoracic sympatheticectomy, and given that certain cardiomyopathies are more likely to affect specific regions of the myocardium, understanding the effect of sympathetic stimulation on regional changes of the normal myocardium, including the RV, becomes important. The myocardial regions where the greatest dispersion occurs can be of particular significance in pathological processes such as sarcoidosis, ARVD, or scars that occur in certain coronary distributions. This study, for the first time, demonstrates that LSG stimulation causes the greatest dispersion on the anterior wall and apex, whereas RSG stimulation causes the greatest dispersion on the RV posterior wall. Previous studies assessing dispersion with RSG stimulation had proved controversial, likely because of small number of electrodes and or lack of sampling of certain regions, such as the RV posterior basal wall. Surprisingly, the regions of greatest dispersion did not occur in areas with the greatest ARI shortening. Although areas with greatest shortening such as LV lateral and posterior wall during LSG stimulation did in fact also show an increase in dispersion, the greatest dispersion was always in regions with the least apparent functional innervation or longest ARIs. This implies that during LSG or RSG functional innervation, significant increases in dispersion may be due to sparse and heterogeneous sympathetic innervation by the particular stellate, in regions where both stellates would normally overlap.

**RSG and LSG stimulation: regional changes and T-wave correlates.** In 1966, Yanowitz et al. (42) demonstrated that right stellactomy had the greatest effect on effective refractory period on the anterior wall, whereas left stellactomy had the greatest effect on the posterior wall. Subsequently, in 1975, Kralios et al. (17) showed that recurrent cardiac nerve stimulation (branch of the RSG) and ventromedial cardiac nerve stimulation (branch of the LSG) lead to shortening of refractory periods of the interventricular septum and anterior wall. The ventrolateral cardiac nerve (another branch of the LSG) produced marked refractory changes on the posterior heart. This same study noted T-wave inversions on a single ECG lead with recurrent and ventromedial cardiac nerve stimulation, whereas ventrolateral cardiac nerve stimulation increased the positivity of the T wave in that lead (17). Armour et al. (2) noted regional changes in myocardial contractility with stimulation of different branches of the stellate ganglia as well as the ganglia itself in the canine heart. The RV showed greater increase in contractility with RSG stimulation, whereas the stimulation of the left ventrolateral cardiac nerve increased contractility in the LV posterior wall. While studying VF intervals in arrested canine hearts during sympathetic stimulation, Ophoth et al. (27) concluded that in some hearts, the effect of LSG was greatest on the posterior wall, whereas in others, a greater effect was seen on the anterior wall. Furthermore, RSG stimulation primarily innervated the anterior wall. Our study confirms these findings in some respects in the porcine model. However, our data demonstrate that the regional changes seen in the porcine model, in contrast to the canine model, may demonstrate less inter-animal variability. We further provide a more detailed regional assessment of functional innervation of the myocardium by the LSG and RSG using the ARI method. Unlike extra-stimulus pacing orVF that can alter autonomic tone, ARI recordings have the advantage of obtaining simultaneous measurements without causing notable changes in sympathetic output. This study demonstrates that nearly all regions of the myocardium are innervated by both LSG and RSG. The regions with the least functional innervation during LSG stimulation were the LV anterior and RV anterior wall and base. The greatest functional innervation occurred on the LV midlateral, posterior wall, and apex. On the other hand, RSG stimulation caused the greatest shortening of ARI on the LV and RV anterior and lateral walls. The fact that LSG provides greater functional innervation to the apex, whereas RSG seems to supply the base of the heart to greater extent than apex, particularly the RV base, is a novel finding in this study and has potential clinical implications. These findings are also in line with mechanical strain data obtained from speckle tracking echocardiography, which show increases in radial and circumferential strain in regions with where we observed the shortest ARIs during LSG and RSG stimulation (45). The epicardial regional RT changes mirror and potentially explain the surface ECG findings, providing further insight into the mechanism of T-wave changes seen with LSG compared with RSG stimulation. The T-wave vector shifts posteriorly in the horizontal plane and inferiorly in the frontal plane during LSG stimulation, in line with the shorter RT at the LV and RV posterior wall and apex. Opposite changes were seen during RSG stimulation, with the T-wave vector directed anteriorly and superiorly, reflecting areas of greatest decrease in RT, which occur on the RV and LV anterior wall and base.

**Limitations.** General anesthetic, isoflurane, can suppress sympathetic nerve activity and could have impacted our results, though we kept the drug concentrations constant and similar across all animals. However, in this study, a strong hemodynamic response was seen during both LSG and RSG stimulation, so it is possible that our results represent a conservative estimate of the true effects of stellate ganglion stimulation. The effects of RSG stimulation on ARI and RT were not corrected for heart rate, since during normal physiological response, RSG stimulation also increases heart rate. Furthermore, any heart rate effects on dispersion are physiologically important. Finally, heart rate would not affect comparison of regional differences in dispersion or shortening seen within RSG stimulation, which was the primary goal of this study. The effect of sympathetic stimulation on endocardial and transmural dispersion was not studied in this model because of the lack of endocardial and intramural recordings. Therefore, this study can only speak to the effect of epicardial dispersion in repolarization on Tp-e interval.

**Conclusions.** This study demonstrates that in an in vivo porcine model with intact autonomic innervation, regional dispersion with LSG stimulation is greatest on the anterior wall of the LV and apex, an area of decreased functional innervation by the LSG, whereas RSG stimulation causes the greatest dispersion on the RV posterior wall and RV posterior base, an
area of decreased functional innervation by the RSG. Moreover, functional regional innervation does not follow a coronary distribution, with myocardial control by LSG and RSG likely representing embryological development of the heart. The regional RT changes provide potential mechanistic insight into the surface ECG T-wave changes noted during adrenergic stimulation. Finally, we find that adrenergic activation increases Tp-e interval, a risk factor for SCD, and the degree of change in global dispersion correlates with the change seen Tp-e, further confirming the myocardial changes consistent with the proarrhythmic effects of adrenergic activation.

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No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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31. *H1030 STELLATE GANGLIA MODULATE REGIONAL DISPERSION AND T-PEAK T-END INTERVAL*


