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## Sympathetic Nerve Stimulation, Not Circulating Norepinephrine, Modulates T-Peak to T-End Interval by Increasing Global Dispersion of Repolarization

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**Background**—T-peak to T-end interval (Tp-e) is an independent marker of sudden cardiac death. Modulation of Tp-e by sympathetic nerve activation and circulating norepinephrine is not well understood. The purpose of this study was to characterize endocardial and epicardial dispersion of repolarization (DOR) and its effects on Tp-e with sympathetic activation.

**Methods and Results**—In Yorkshire pigs (n=13), a sternotomy was performed and the heart and bilateral stellate ganglia were exposed. A 56-electrode sock and 64-electrode basket catheter were placed around the epicardium and in the left ventricle (LV), respectively. Activation recovery interval, DOR, defined as variance in repolarization time, and Tp-e were assessed before and after left, right, and bilateral stellate ganglia stimulation and norepinephrine infusion. LV endocardial and epicardial activation recovery intervals significantly decreased, and LV endocardial and epicardial DOR increased during sympathetic nerve stimulation. There were no LV epicardial versus endocardial differences in activation recovery interval during sympathetic stimulation, and regional endocardial activation recovery interval patterns were similar to the epicardium. Tp-e prolonged during left (from 40.4±2.2 ms to 92.4±12.4 ms;  $P<0.01$ ), right (from 47.7±2.6 ms to 80.7±11.5 ms;  $P<0.01$ ), and bilateral (from 47.5±2.8 ms to 78.1±9.8 ms;  $P<0.01$ ) stellate stimulation and strongly correlated with whole heart DOR during stimulation ( $P<0.001$ ,  $R=0.86$ ). Of note, norepinephrine infusion did not increase DOR or Tp-e.

**Conclusions**—Regional patterns of LV endocardial sympathetic innervation are similar to that of LV epicardium. Tp-e correlated with whole heart DOR during sympathetic nerve activation. Circulating norepinephrine did not affect DOR or Tp-e. (*Circ Arrhythm Electrophysiol.* 2015;8:174-185. DOI: 10.1161/CIRCEP.114.002195.)

**Key Words:** action potential ■ autonomic nervous system ■ dispersion ■ ECG ■ sympathetic ■ T wave

The increased spatial heterogeneity and dispersion of ventricular repolarization caused by activation of the cardiac sympathetic nervous system may lead to ventricular arrhythmias and sudden cardiac death.<sup>1-3</sup> Selective modulation of cardiac sympathetic nerves has been proposed as an alternative option for patients with recurrent ventricular arrhythmias, despite optimal medical therapy and catheter ablation.<sup>4-6</sup> The time interval from the peak to the end of the electrocardiographic T wave (Tp-e) is an independent predictor of sudden cardiac death in experimental models of long QT and in patients with long QT syndrome,<sup>7,8</sup> Brugada syndrome,<sup>9</sup> hypertrophic cardiomyopathy,<sup>10</sup> and structural heart disease.<sup>11-13</sup> Tp-e is also thought to represent a marker of transmural dispersion of repolarization (TDR).<sup>7,14,15</sup> However, it has also been reported that Tp-e reflects not only TDR, but also whole heart dispersion of repolarization (DOR).<sup>16,17</sup> Sympathetic nerve stimulation increases dispersion in activation recovery interval (ARI),<sup>18,19</sup> a surrogate

marker of local action potential duration.<sup>20</sup> Little is known about the effects of circulating catecholamines compared with sympathetic nerve activation on Tp-e and DOR. In addition, regional endocardial effects in vivo are not well understood given that previous studies had focused primarily on epicardial recordings.

The purpose of this study was to (1) evaluate effects of sympathetic activation by direct nerve stimulation versus increased circulating norepinephrine on Tp-e and epicardial and endocardial ARI and DOR and (2) identify any differences in functional distribution of sympathetic innervation of the LV epicardium versus endocardium.

### Methods

#### Surgical Preparation

Animal handling and care was approved by the University of California Institutional Animal Care and Use Committee and

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### WHAT IS KNOWN

- Sympathetic activation increases the risk of ventricular tachy-arrhythmias and sudden cardiac death.
- T-peak to T-end interval is an independent marker of sudden cardiac death.
- Sympathetic nerve stimulation increases dispersion of repolarization.
- Stimulation of the left stellate ganglion causes greater shortening of action potential duration of the epicardial posterior/dorsal and apical ventricular walls, whereas stimulation of the right stellate ganglion causes greater shortening of action potential duration of the epicardial anterior/ventral and basal walls.

### WHAT THE STUDY ADDS

- T-peak to T-end interval was increased by sympathetic nerve stimulation, but not by the circulating catecholamine, norepinephrine.
- The increase in T-peak to T-end interval correlates significantly with the increase in ventricular dispersion of repolarization caused by sympathetic nerve stimulation, but not norepinephrine.
- Endocardial left ventricular regional patterns of functional innervation by the left and right stellate ganglia follow that of the epicardium.

performed in accordance with National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

Female Yorkshire pigs ( $n=13$ ,  $44.9\pm 3.9$  kg) were sedated (telazol [8–10 mg/kg] and fentanyl [2–4  $\mu\text{g/kg}$ ]), intubated, and mechanically ventilated. General anesthesia was maintained with inhaled isoflurane (0.8%–1.5%) and intermittently timed boluses of fentanyl. Femoral arterial access and venous access along with left carotid arteriotomy and jugular venotomy were performed. A median sternotomy was performed to expose the heart and bilateral cervicothoracic stellate ganglia (SG). Customized bipolar needle electrodes were placed through the right and left SG for stimulation. Then, anesthesia with inhaled isoflurane was switched to continuous intravenous infusion of  $\alpha$ -chloralose (10 mg/kg/h). Hemodynamic parameters were continuously monitored, and arterial blood gas levels were checked at regular interval. After surgical preparation, animals were stabilized for 1 hour before initiation of experimental protocol. Animals were euthanized by intravenous administration of a lethal dose of potassium chloride and sodium pentobarbital (100 mg/kg).

### Stellate Ganglia Stimulation

The left, right, and bilateral SG were electrically stimulated (4 ms pulses, 4 Hz) by a Grass stimulator (Model S88; Grass Technologies, West Warwick, RI) for 30 seconds. The threshold current, set at a 10% increase in systolic blood pressure, was measured for each SG. The stimulation current was programmed at twice the threshold for each SG. Left stellate ganglion stimulation (LSS), right stellate ganglion stimulation (RSS), and bilateral SG stimulation (BSS) were performed in all animals with a 20-minute interval between stimulations.

### Norepinephrine Infusion

After SG stimulation and a minimum of a 20 minutes wait period, norepinephrine was infused continuously for 2 minutes at 0.3  $\mu\text{g/kg}$ /

min. Hemodynamic and ARI parameters were analyzed just before infusion and at 1 and 2 minutes during the infusion. Both 1 minute and 2 minutes intervals were analyzed to assure that norepinephrine effects were consistent and had reached steady state levels. Norepinephrine instead of epinephrine was used given that it is the endogenous neurotransmitter of cardiac sympathetic nerves and for comparison with effects of direct nerve stimulation.

### Hemodynamic and Surface ECG Recordings

Blood pressure was continuously recorded via a femoral arterial catheter. Heart rate (HR) and 12 lead electrocardiograms (ECG) were continuously obtained. Limb leads were placed in standard positions. Because of the open-chest surgical procedure, precordial lead electrodes were placed posteriorly in the positions of V6 through V11. Tp-e was measured in the inferior limb leads with the clearest T wave recording. The peak of the T wave was visually defined, and the end of T wave was defined as the intersection of the tangent to the slope of the T wave and the isoelectric line<sup>11,21</sup> at 100 mm/s sweep speed. The T p-e interval was measured in the inferior limb lead with the clearest recording at a sweep speed at 200 mm/s. The same limb lead was used at baseline and during peak sympathetic stimulation, and the longest T p-e interval during stimulation (which usually occurred at 15 seconds into stimulation and lasted to 30 seconds) was measured.

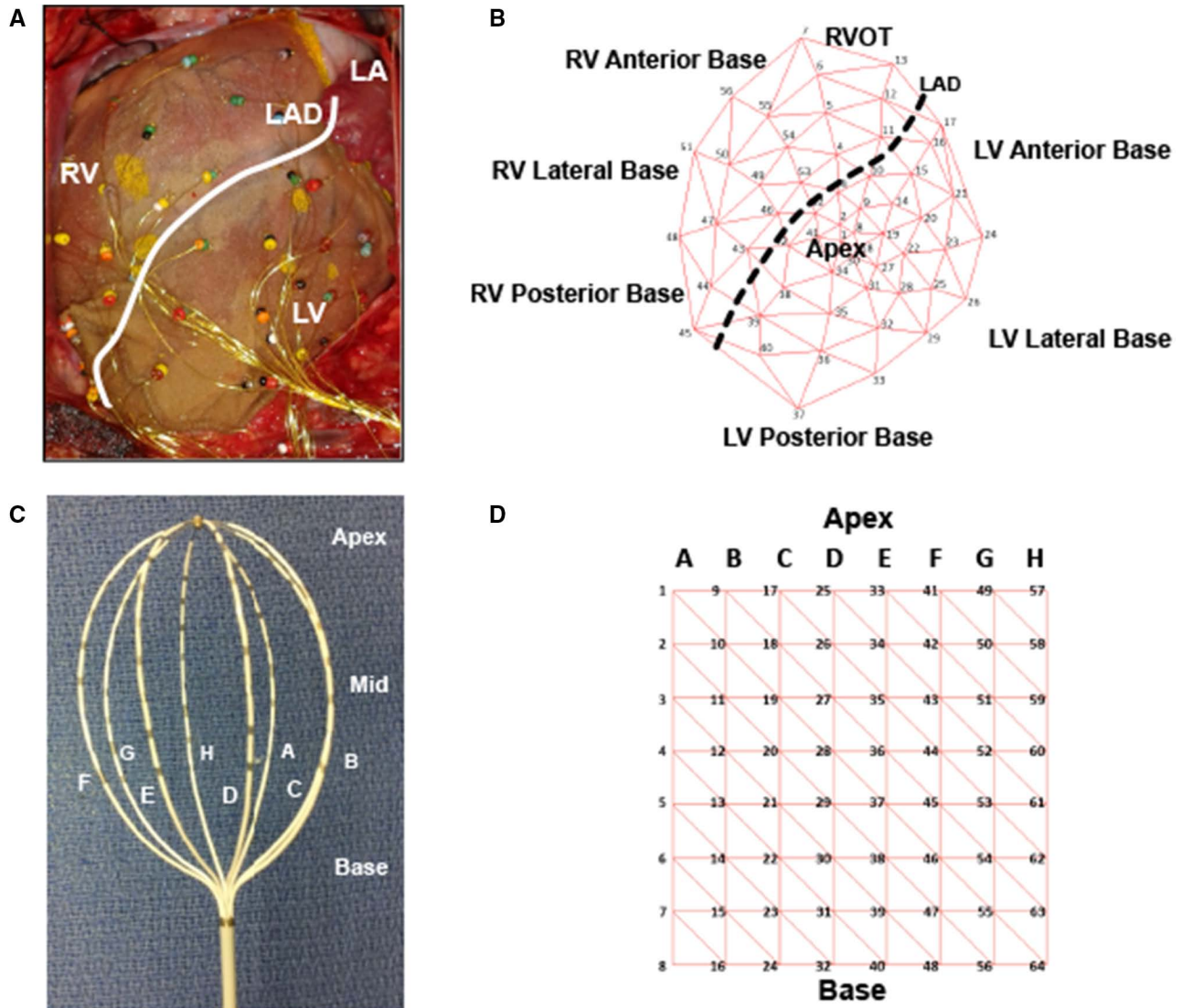
### Activation Recovery Interval Measurements

ARI has been shown to correlate with local action potential duration and monophasic action potential duration recordings.<sup>20,22</sup> Activation time (AT) and repolarization time (RT) were measured from unipolar electrograms (0.05–500 Hz) as the intervals from onset to the minimal  $dV/dt$  of the depolarization wave and from the onset to the maximal  $dV/dt$  of the repolarization wave (T wave), respectively. The difference, ARI, reflects action potential duration at the electrode site ( $\text{ARI}=\text{RT}-\text{AT}$ ).<sup>20,22</sup> ARI analysis was performed via customized software (Scaldyn M, University of Utah, Salt Lake City, UT).

For purposes of this article, anterior refers to the ventral and posterior refers to the dorsal aspect of the animal. For epicardial ARI analysis, a customized 56-electrode sock was placed around the ventricles (Figure 1A and 1B). Epicardial electrograms were recorded using a custom-made 128 channel multiplexor (University of Utah, Salt Lake City, Utah). ARI data from 56-electrode sock were projected onto a 2-dimensional (2D) polar map by using publicly available software (Map3d; Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, UT; <http://www.sci.utah.edu/cibc/software/107-map3d.html>). For regional epicardial analysis, sock electrodes on the LV epicardium were grouped into 4 regions: apex, anterior wall, lateral wall, and posterior wall.

For LV endocardial ARI analysis, a 64-electrode basket catheter (Constellation catheter, 48 mm diameter, 4 mm spacing; Boston Scientific, Minneapolis, MN) was inserted into the LV via the left carotid artery sheath under ultrasound guidance (Figure 1C). Endocardial unipolar electrograms were recorded using a Prucka CardioLab System (GE Healthcare, Waukesha, WI). Position of the basket catheter was delineated using a 3D electroanatomic mapping system (Ensite; St. Jude Medical, Minneapolis, MN). The 8 splines of the catheter were divided into septal, anterior, lateral, and posterior walls depending on their location/contact. The basket catheter electrodes were also separated into apical (distal 2 electrodes), mid (middle 3 electrodes), and basal (proximal 3 electrodes). For mapping and visualization of regional endocardial ARI patterns, the recordings from the 64-electrodes of the basket catheter were mapped onto a 2D plaque polar map using Map3d (Figure 1D). Electrograms with biphasic repolarization waves or noise were excluded from analysis. For comparison of epicardial versus endocardial differences in ARI and RT, electrodes on the sock directly across from electrodes of the endocardial basket catheter were manually selected and compared for each region.

Dispersion in RT (DOR) and ARI were calculated as variance in RTs and ARIs measured across all electrodes in a specific region or



**Figure 1.** A, A 56-electrode sock is placed over the ventricles for recording of epicardial electrograms. B, Sock electrode configuration for creation of polar maps is shown. C, The 64-electrode catheter used for endocardial recordings is shown. D, The basket catheter splines are placed on a 2-dimensional plaque-type configuration for polar map visualization. LA indicates left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle; and RVOT, right ventricular outflow tract.

the entire epicardium and LV endocardium (whole heart). Transmural differences in ARI of the LV were calculated as mean LV epicardial ARI minus mean LV endocardial ARI (transmural difference in ARI =  $ARI_{epicardium} - ARI_{endocardium}$ ). The change in DOR and Tp-e was also analyzed to account for baseline differences.

**Statistical Analysis**

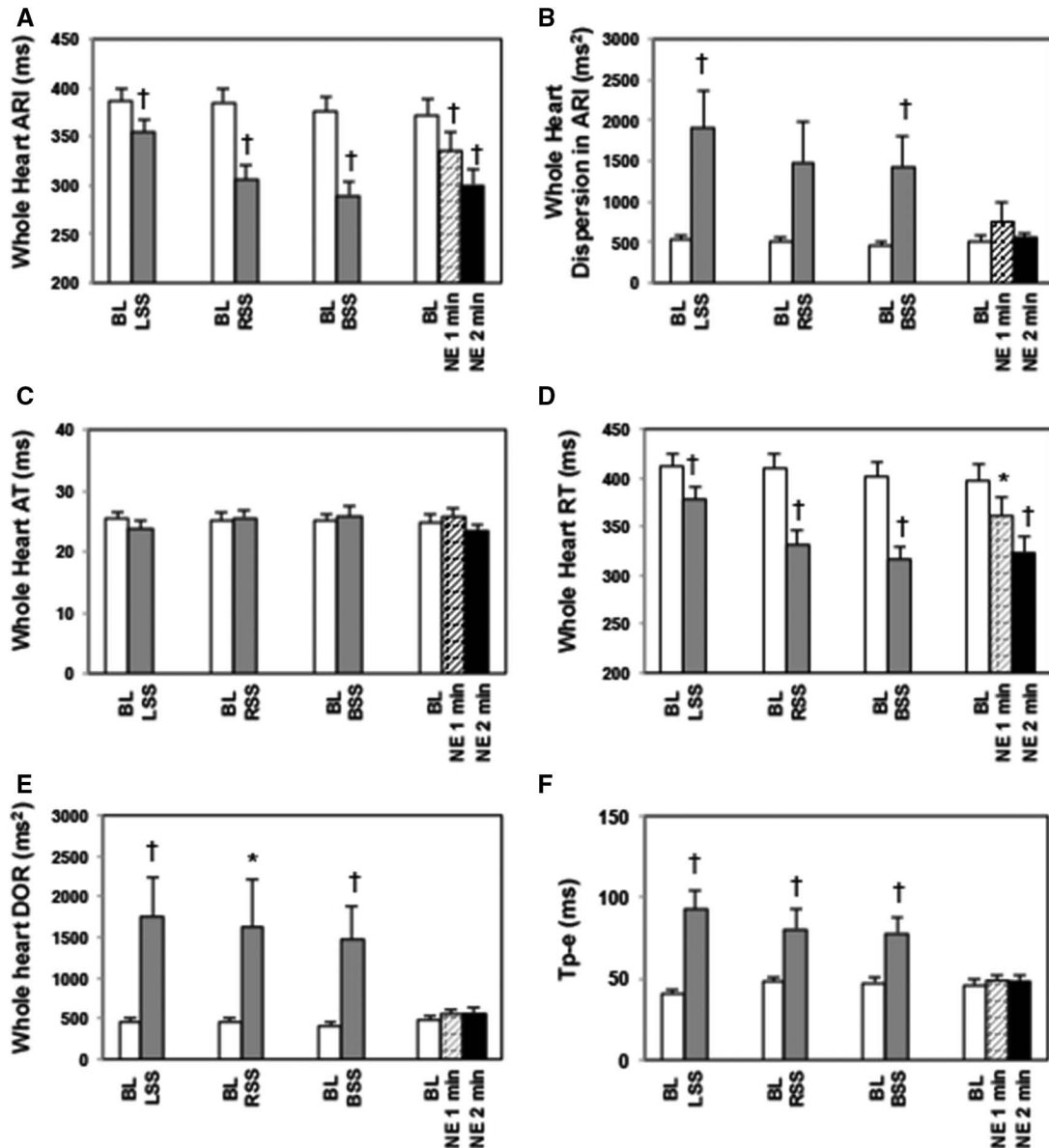
All values are expressed as mean±SEM. For paired comparison of baseline and intervention, the Wilcoxon signed-rank test was used given the non-Gaussian distribution of the data. Regional comparisons during LSS, RSS, BSS, and norepinephrine infusion were performed using linear mixed effects regression models with heterogeneous variances across regions. For comparison of the correlation between Tp-e and DOR, Pearson product-moment correlation coefficient was used. The Benjamini–Hochberg procedure was used to evaluate significance at 5% false discovery rate for each experiment. A P value <0.05 was considered statistically significant. All P values <0.05 remained significant after controlling the false discovery rate at 5%. Analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC).

**Results**

A total of 13 animals successfully underwent the study protocol. Current of stimulation was 6.5±0.86 mA for LSS and 4.9±0.6 mA for RSS.

**Effects of Sympathetic Activation on Hemodynamic Parameters**

There was no significant increase in HR during LSS (71.7±2.3 beats per minute versus 73.8±3.0 beats per minute; P=0.65), whereas RSS and BSS significantly increased HR (from 72.5±2.3 beats per minute to 99.0±5.3 beats per minute, P<0.01; and from 74.0±2.7 beats per minute to 91.0±4.7 beats per minute, P<0.01, respectively). HR was also significantly increased during norepinephrine infusion at 2 minutes (from 74.4±2.9 beats per minute to 87.2±4.4 beats per minute, P<0.01), with no significant increase at 1 minute (82.3±5.0 beats per minute, P=0.06).



**Figure 2.** Effects of stellate ganglia (SG) stimulation and norepinephrine (NE) infusion on whole heart mean activation recovery interval (ARI; **A**), dispersion in ARI (**B**), activation time (AT; **C**), repolarization time (RT; **D**), dispersion of repolarization (DOR; **E**), and T-peak to T-end interval (Tp-e) interval (**F**) are shown. Both sympathetic nerve stimulation and NE infusion decrease mean ARI. However, only stellate ganglion stimulation increased DOR and Tp-e. \* $P < 0.05$  for baseline vs SG stimulation or NE infusion. † $P < 0.01$  for baseline vs SG stimulation or NE infusion.  $P$  values obtained using the Wilcoxon signed-rank test. BL indicates baseline; BSS, bilateral stellate stimulation; LSS, left stellate stimulation; and RSS, right stellate stimulation.

Systolic blood pressure was significantly increased during LSS (from  $124.5 \pm 5.1$  mmHg to  $140.2 \pm 5.5$  mmHg,  $P < 0.01$ ), RSS (from  $123.0 \pm 5.7$  mmHg to  $142.9 \pm 5.6$  mmHg,  $P < 0.01$ ), and BSS (from  $123.5 \pm 6.0$  mmHg to  $154.3 \pm 6.4$  mmHg,  $P < 0.01$ ). Systolic blood pressure was also increased by norepinephrine infusion at 1 minute (from  $121.5 \pm 6.6$  mmHg to  $144.1 \pm 6.9$  mmHg,  $P < 0.01$ ) and 2 minutes (to  $157.5 \pm 5.9$  mmHg,  $P < 0.01$ ).

### Effects of Sympathetic Activation on Global ARIs and Tp-e

Effects of SG stimulation and norepinephrine infusion on whole heart ARI are shown in Figure 2. Whole heart ARI was significantly shortened during LSS (from  $385.6 \pm 13.8$

ms to  $354.3 \pm 12.5$  ms,  $P < 0.01$ ), RSS (from  $384.9 \pm 14.2$  ms to  $305.1 \pm 15.9$  ms,  $P < 0.01$ ), and BSS (from  $375.6 \pm 15.6$  ms to  $289.8 \pm 13.4$  ms,  $P < 0.01$ ). AT was unchanged during LSS ( $25.3 \pm 0.9$  ms versus  $23.6 \pm 1.4$  ms,  $P = 0.09$ ), RSS ( $25.1 \pm 1.3$  ms versus  $25.6 \pm 1.1$  ms,  $P = 0.35$ ), or BSS ( $25.1 \pm 1.0$  ms versus  $25.6 \pm 1.7$  ms,  $P = 0.76$ ). Therefore, as with ARI, RT was decreased during LSS (from  $411.0 \pm 14.1$  ms to  $377.9 \pm 13.1$  ms,  $P < 0.01$ ), RSS (from  $409.9 \pm 14.7$  ms to  $330.6 \pm 15.9$  ms,  $P < 0.01$ ), and BSS (from  $400.7 \pm 16.1$  ms to  $315.5 \pm 13.2$  ms,  $P < 0.01$ ). Whole heart DOR was significantly increased during LSS (from  $460.8 \pm 39.6$  ms<sup>2</sup> to  $1761.0 \pm 470.5$  ms<sup>2</sup>,  $P < 0.01$ ), RSS (from  $468.4 \pm 33.8$  ms<sup>2</sup> to  $1633.6 \pm 573.9$  ms<sup>2</sup>,  $P = 0.013$ ), and BSS (from  $417.2 \pm 29.3$  ms<sup>2</sup> to  $1468.6 \pm 410.2$  ms<sup>2</sup>,  $P < 0.01$ ; Figure 2E). Tp-e was significantly prolonged during LSS (from

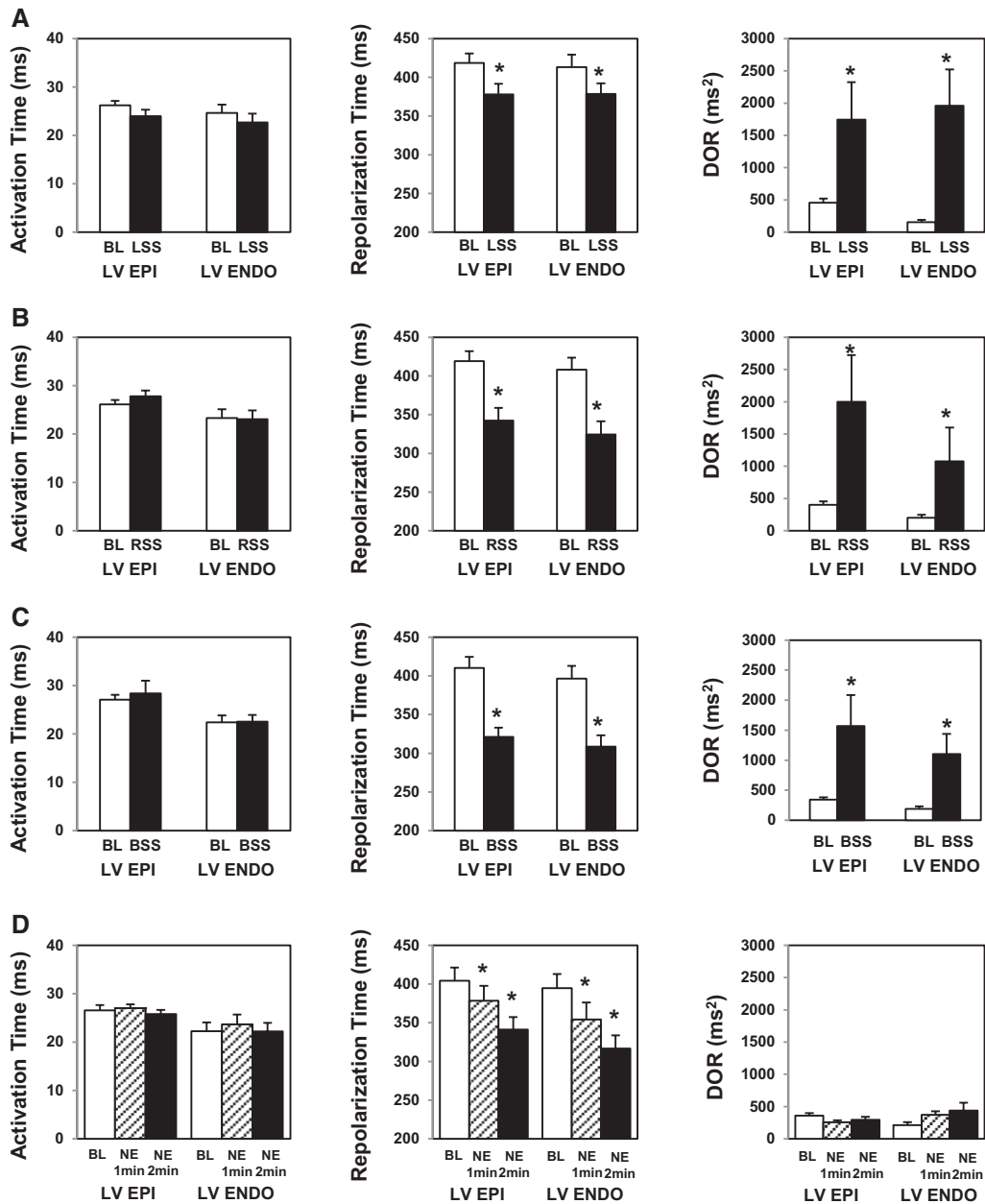
40.4±2.2 ms to 92.4±12.4 ms,  $P<0.01$ ), RSS (from 47.7±2.6 ms to 80.7±11.5 ms,  $P<0.01$ ), and BSS (from 47.5±2.8 ms to 78.1±9.8 ms,  $P<0.01$ ; Figure 2F).

Whole heart ARI also shortened with norepinephrine infusion (from 372.2±17.4 ms to 335.4±19.5 ms at 1 minute,  $P<0.01$ , and to 300.5±15.9 ms at 2 minutes,  $P<0.01$ ), whereas AT remained unchanged (24.8±1.3 ms versus 25.7±1.3 ms at 1 minute,  $P=0.29$ , versus 23.4±1.1 ms at 2 minutes,  $P=0.06$ ). Therefore, RT was also significantly decreased with norepinephrine infusion (from 396.9±17.9 ms to 361.1±20.0 ms at 1 minute,  $P<0.01$ , to 323.9±16.5 ms at 2 minutes,  $P<0.01$ ). There was no significant increase in DOR (Figure 2E). Furthermore, Tp-e was also not

significantly increased during norepinephrine infusion (Figure 2F).

**Effects of Stellate Ganglion Stimulation on LV Endocardial and Epicardial ARI**

ARI significantly shortened on the LV endocardium and LV epicardium during LSS (from 388.6±15.9 ms to 355.7±14.0 ms on the endocardium,  $P<0.01$ , and from 392.4±11.8 ms to 353.8±12.8 ms on the epicardium,  $P<0.01$ ), RSS (from 388.2±16.4 ms to 304.9±17.0 ms on the endocardium,  $P<0.01$ , and from 392.9±12.6 ms to 314.6±15.6 ms on the epicardium,  $P<0.01$ ), and BSS (from 378.1±17.4 ms to 289.9±15.3 ms on the endocardium,  $P<0.01$ , and

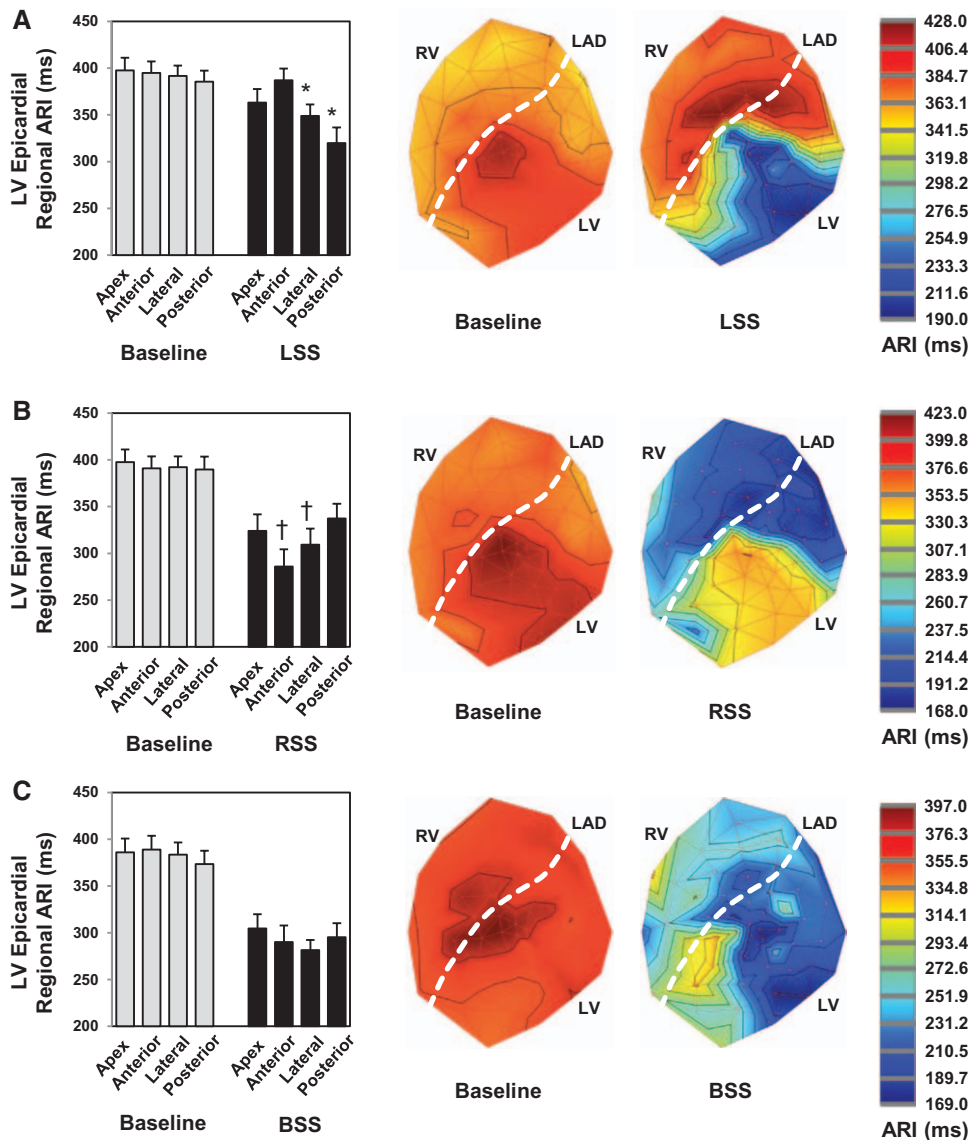


**Figure 3.** Effects of LSS (A), RSS (B), BSS (C), and NE infusion (D) on activation time (AT), repolarization time (RT), and dispersion of repolarization (DOR) of left ventricular (LV) epicardium and endocardium. \* $P<0.01$  for baseline vs stellate ganglion stimulation or NE administration. ARI indicates activation recovery interval; BL, baseline; BSS, bilateral stellate stimulation; Epi, epicardium; Endo, endocardium; LSS, left stellate stimulation; NE, norepinephrine infusion; and RSS, right stellate stimulation.  $P$  values obtained using the Wilcoxon signed-rank test.

from  $383.0 \pm 14.1$  ms to  $292.7 \pm 12.5$  ms on the epicardium,  $P < 0.01$ ). ARI dispersion increased on the LV endocardium and epicardium during LSS ( $216.6 \pm 65.7$  ms<sup>2</sup> versus  $1756.9 \pm 459.3$  ms<sup>2</sup> on the endocardium,  $P < 0.01$ , and  $431.8 \pm 75.5$  ms<sup>2</sup> versus  $1880.8 \pm 624.5$  ms<sup>2</sup> on the epicardium,  $P < 0.01$ ), RSS ( $205.0 \pm 41.6$  ms<sup>2</sup> versus  $1345.5 \pm 572.2$  ms<sup>2</sup> on the endocardium,  $P < 0.01$ , and  $365.7 \pm 47.1$  ms<sup>2</sup> versus  $1689.6 \pm 618.4$  ms<sup>2</sup> on the epicardium,  $P = 0.027$ ), and BSS ( $194.8 \pm 46.1$  ms<sup>2</sup> versus  $1230.8 \pm 401.5$  ms<sup>2</sup> on the endocardium,  $P < 0.01$ , and  $354.6 \pm 43.3$  ms<sup>2</sup> versus  $1446.5 \pm 453.7$  ms<sup>2</sup> on the epicardium,  $P < 0.01$ ).

AT was unchanged on the LV endocardium or epicardium during LSS ( $24.6 \pm 1.7$  ms versus  $22.7 \pm 1.8$  ms on the endocardium,  $P = 0.08$ , and  $26.2 \pm 0.9$  versus  $24.0 \pm 1.3$  ms on the epicardium,  $P = 0.08$ ), RSS ( $23.3 \pm 1.8$  ms versus  $23.0 \pm 1.8$  ms

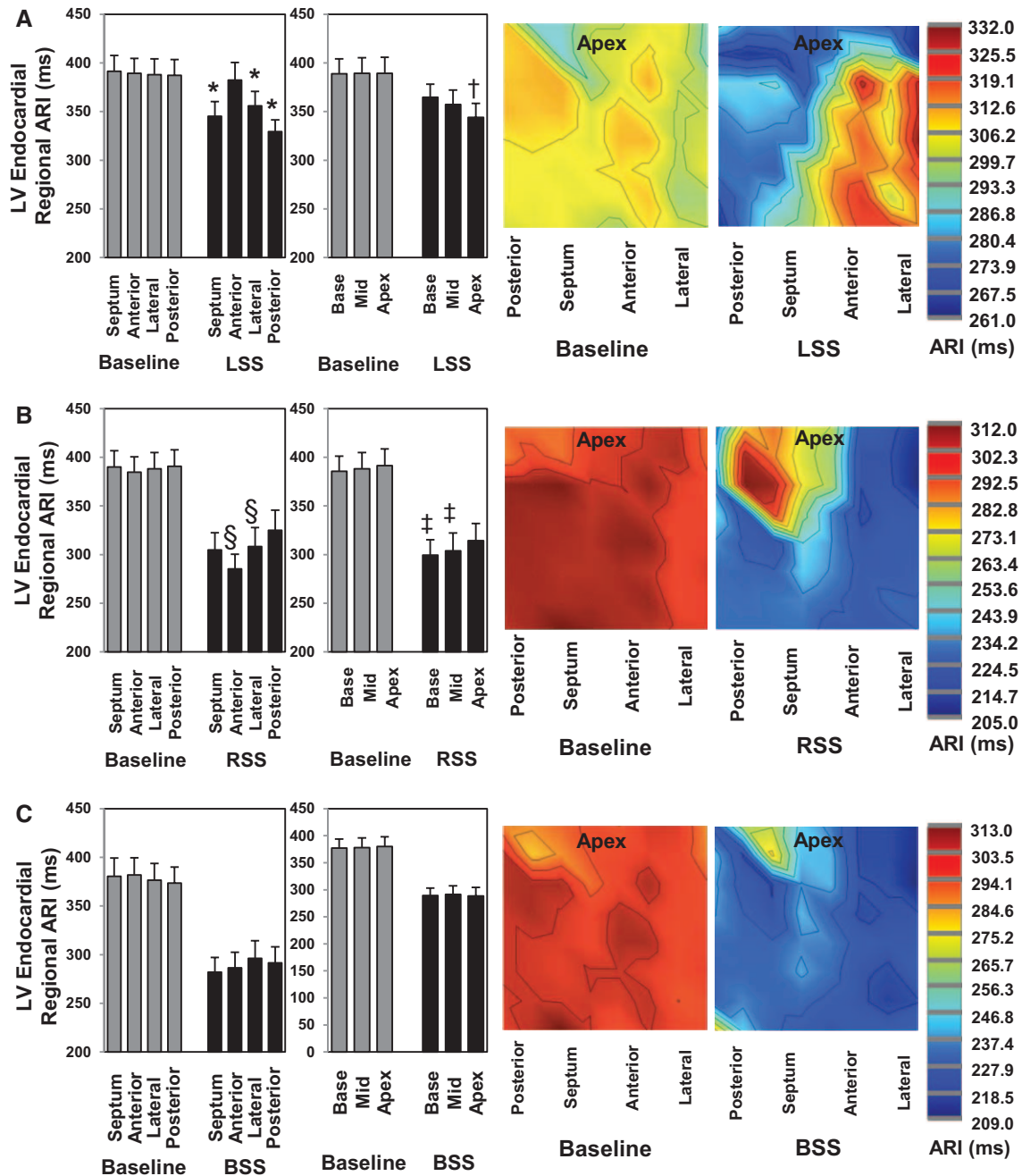
on the endocardium,  $P = 0.69$ , and  $26.1 \pm 0.9$  versus  $27.8 \pm 1.2$  ms on the epicardium,  $P = 0.06$ ), or BSS ( $22.4 \pm 1.5$  ms versus  $22.5 \pm 1.4$  ms on the endocardium,  $P = 0.95$ , and  $27.1 \pm 1.0$  ms versus  $28.3 \pm 2.7$  ms on the epicardium,  $P = 0.74$ ). Therefore, as with ARI, RT was significantly decreased by LSS (from  $413.2 \pm 16.0$  ms to  $378.4 \pm 14.0$  ms on the endocardium,  $P < 0.01$ , and from  $418.6 \pm 12.2$  ms to  $377.8 \pm 13.8$  ms on the epicardium,  $P < 0.01$ ), RSS (from  $411.5 \pm 16.5$  ms to  $327.9 \pm 16.7$  ms on the endocardium,  $P < 0.01$ , and from  $419.0 \pm 13.1$  ms to  $342.4 \pm 16.2$  ms on the epicardium,  $P < 0.01$ ) and BSS (from  $400.5 \pm 17.4$  ms to  $312.4 \pm 15.0$  ms on the endocardium,  $P < 0.01$ , and from  $410.1 \pm 14.6$  ms to  $321.0 \pm 12.1$  ms on the epicardium,  $P < 0.01$ ). As with ARI dispersion, LV epicardial and endocardial DOR was significantly increased by right, left, and bilateral SG stimulation (Figure 3).



**Figure 4.** Regional epicardial activation recovery interval (ARI) effects of LSS (A), RSS (B), and BSS (C) are shown in the left panels, whereas the right panels demonstrate a polar map from a representative animal during each condition. \* $P < 0.01$  for comparison of mean ARI of the left ventricular (LV) anterior wall to other regions. † $P < 0.01$  for comparison of mean ARI of LV posterior wall to other regions. BSS indicates bilateral stellate stimulation; LAD, left anterior descending coronary artery; LSS, left stellate stimulation; RSS, right stellate stimulation; and RV, right ventricle. Regional comparisons performed using the linear mixed effects regression model with heterogeneous variances.

ARI was also decreased on the LV endocardium and epicardium during norepinephrine infusion (from  $376.2 \pm 18.8$  ms to  $330.0 \pm 21.5$  ms at 1 minute,  $P < 0.01$ , to  $293.3 \pm 16.2$  ms at 2 minutes,  $P < 0.01$  on the endocardium, and from  $377.7 \pm 16.5$  ms to  $351.2 \pm 19.0$  ms at 1 minute,  $P < 0.01$ , to  $315.4 \pm 15.6$  ms at 2 minutes;  $P < 0.01$  on the epicardium). There was no significant change in AT of the endocardium or epicardium ( $22.2 \pm 1.8$  ms versus  $23.7 \pm 2.0$  ms at 1 minute,  $P = 0.16$ , versus  $22.2 \pm 1.8$  ms at 2 minutes,  $P = 0.96$  on the endocardium,  $26.5 \pm 1.1$  ms versus

$27.0 \pm 0.8$  ms at 1 minute,  $P = 0.65$ , versus  $25.8 \pm 0.8$  ms at 2 minutes;  $P = 0.43$  on the epicardium). Therefore, RT was also decreased during norepinephrine infusion (from  $398.5 \pm 19.0$  ms to  $353.7 \pm 21.8$  ms at 1 minute,  $P < 0.01$ , to  $315.5 \pm 16.6$  ms at 2 minutes,  $P < 0.01$  on the endocardium, from  $404.3 \pm 17.0$  ms to  $378.2 \pm 19.4$  ms at 1 minute,  $P < 0.01$ , to  $341.2 \pm 16.2$  ms at 2 minutes,  $P < 0.01$  on the epicardium). However, norepinephrine infusion did not significantly increase ARI dispersion, LV epicardial, or endocardial DOR (Figure 3D).



**Figure 5.** Regional endocardial activation recovery interval (ARI) effects of LSS (A), RSS (B), and BSS (C) are shown in the left panels, whereas the right panels demonstrate a representative ARI polar maps from a single animal. \* $P < 0.05$  for comparison of mean ARI of the anterior wall to other regions.  $\$P < 0.05$  for comparison of mean ARI of the posterior wall to other regions. † $P < 0.01$  when comparing apical ARI with mid wall or basal ARIs during LSS. ‡ $P < 0.05$  for comparison of apical with mid wall or basal ARIs during RSS. Regional comparisons performed using the linear mixed effects model with heterogeneous variances. BSS indicates bilateral stellate stimulation; LSS, left stellate stimulation; LV, left ventricle; and RSS, right stellate stimulation.



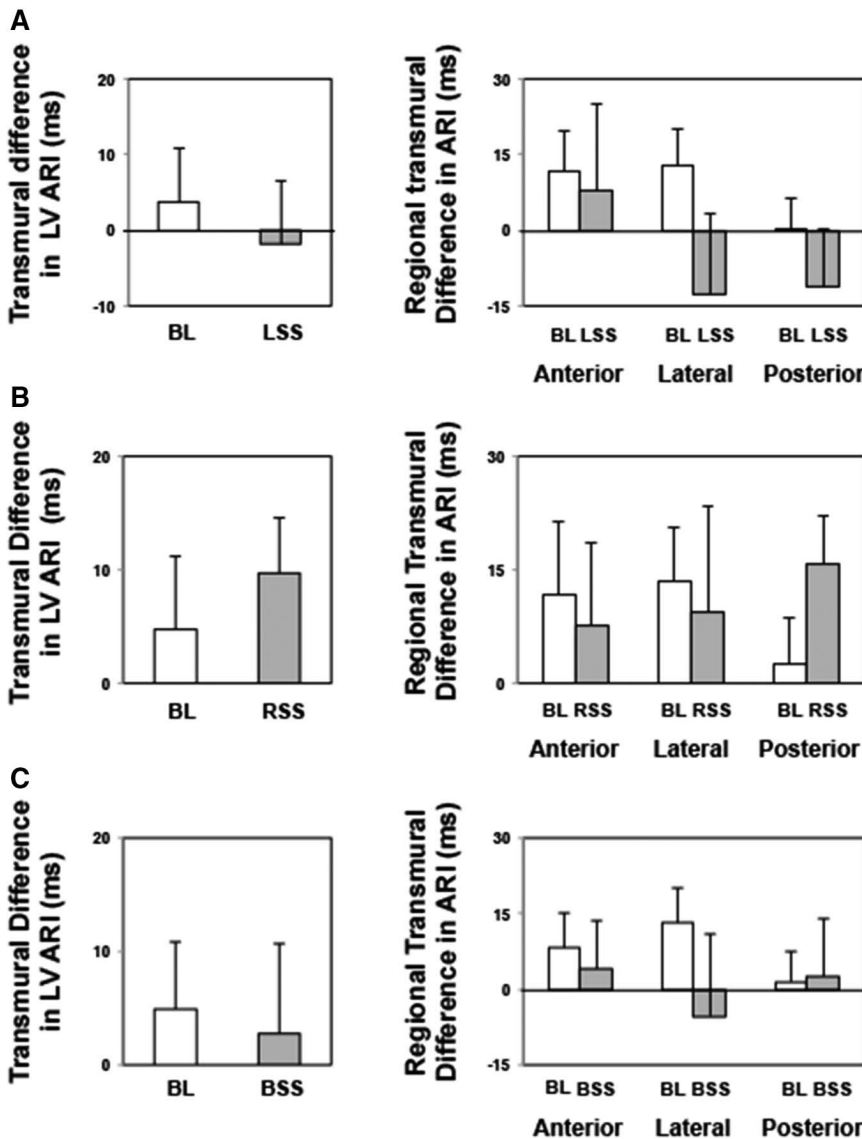
**Effects of Stellate Ganglion Stimulation on Regional ARI**

Before SG stimulation, there was no significant difference in regional ARIs of the epicardium. During LSS, LV epicardial ARI on the posterior and lateral walls shortened more than the anterior wall (Figure 4A), whereas greater ARI shortening was observed on the anterior wall compared with the posterior wall during RSS (Figure 4B). Of note, there was no significant regional ARI differences during BSS (Figure 4C).

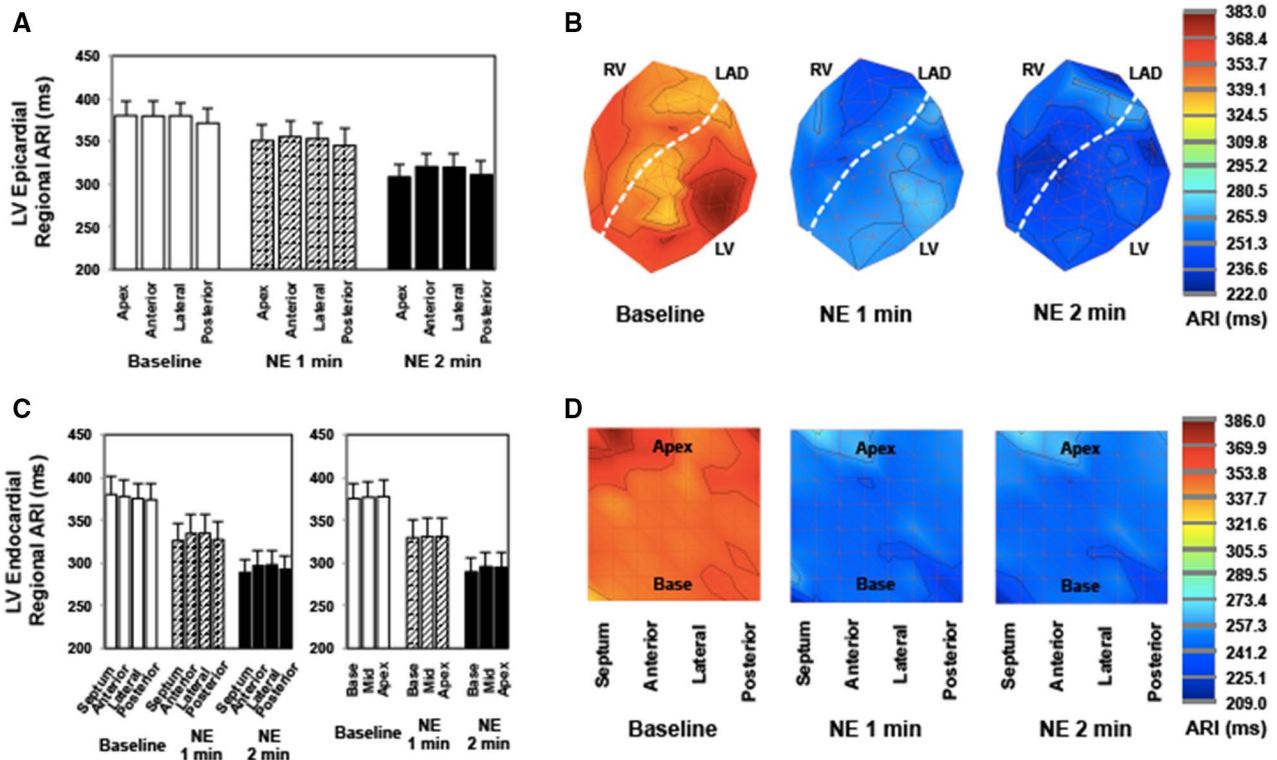
Similar to the epicardium, before LSS, RSS, or BSS, there were no significant regional differences in mean ARIs of the LV endocardium. During LSS, LV endocardial ARI was significantly shorter on the posterior wall, lateral wall, and septum compared with the anterior wall (Figure 5A),  $P < 0.01$ . LSS significantly shortened ARI of the apex (from  $389.4 \pm 16.3$  ms to  $344.0 \pm 14.5$  ms) more than the base (from  $388.8 \pm 15.5$  ms to  $364.7 \pm 13.4$  ms,  $P < 0.001$  for apex versus base).

On the other hand, during RSS, LV endocardial ARI was significantly shorter on the anterior wall (from  $384.8 \pm 15.8$  ms to  $285.2 \pm 15.1$  ms) compared with the posterior wall (from  $390.6 \pm 16.9$  ms to  $324.9 \pm 20.7$  ms,  $P = 0.003$  for anterior versus posterior). In addition, LV endocardial ARI was significantly shorter on the lateral wall (from  $388.2 \pm 16.5$  ms to  $308.3 \pm 19.3$  ms) compared with posterior wall ( $P = 0.011$  for lateral versus posterior). There were no significant differences in endocardial ARI of the septum ( $390.0 \pm 16.8$  ms to  $304.7 \pm 17.7$  ms) versus the posterior wall ( $P = 0.1$  for septum versus posterior wall). RSS shortened LV endocardial ARI of the basal walls (from  $385.6 \pm 15.6$  ms to  $299.4 \pm 15.8$  ms) more than the apex (from  $391.5 \pm 17.0$ – $314.4 \pm 17.5$  ms,  $P = 0.018$  for base versus apex; Figure 5B). There was a trend for greater shortening of the mid wall compared with the apex as well (from  $388.2 \pm 16.7$  ms to  $303.9 \pm 18.3$  ms on the mid wall,  $P = 0.06$ ). There was no significant difference in regional apico-basal ARIs during BSS (Figure 5C).

At baseline, no significant differences in epicardial ARI compared with endocardial ARI were observed ( $389.4 \pm 7.3$



**Figure 6.** There is no effect on global or regional LV transmural differences in activation recovery interval (ARI) during LSS (A), RSS (B), and BSS (C). The Wilcoxon signed-rank test was used for the comparison of the transmural differences in ARI. The mixed effects model with heterogeneous variances was used for comparison of regional transmural differences in ARI. BL indicates baseline; BSS, bilateral stellate stimulation; LSS, left stellate stimulation; LV, left ventricle; and RSS, right stellate stimulation.



**Figure 7.** Regional epicardial activation recovery intervals (ARIs) for all animals (A) and representative polar maps at baseline and during NE infusion at 1 minute and 2 minutes (B). Regional endocardial ARIs (C) and representative polar maps during NE infusion (D). The mixed effects model with heterogeneous variances was used for comparison of regional differences in ARI. LAD indicates left anterior descending coronary artery; LV, left ventricle; NE, norepinephrine infusion; and RV, right ventricle.

ms versus  $385.0 \pm 9.3$  ms,  $P=0.25$ ). Transmural difference in ARI was not changed by LSS ( $3.8 \pm 7.0$  ms at baseline versus  $-1.8 \pm 8.4$  ms during LSS,  $P=0.54$ ), RSS ( $4.7 \pm 6.6$  ms at baseline versus  $9.7 \pm 4.9$  ms during RSS,  $P=0.46$ ), or BSS ( $4.9 \pm 6.0$  ms at baseline versus  $2.8 \pm 8.0$  ms during BSS,  $P=0.89$ ; Figure 6).

**Effects of Norepinephrine Infusion on ARI and DOR**

Before norepinephrine infusion, no significant difference in regional ARI of the LV epicardium versus endocardium was observed. ARI was significantly shortened at 1 and 2 minutes after norepinephrine administration on both the epicardium and endocardium without significant regional (Figure 7).

**Relationship Between Tp-e and DOR**

The relationship between Tp-e and DOR is shown in Figure 8. No significant correlation between Tp-e and whole heart DOR was found at baseline ( $R=0.12$ ,  $P=0.47$ ). However, Tp-e was strongly correlated with whole heart DOR during stimulation ( $R=0.86$ ,  $P<0.001$ ). This correlation was strong for both LV epicardial ( $R=0.82$ ,  $P<0.001$ ) and LV endocardial DOR ( $R=0.89$ ,  $P<0.001$ ). The change in Tp-e was also strongly correlated with the change in whole heart DOR ( $R=0.70$ ,  $P<0.001$ ). Transmural differences in RT had the weakest correlation with Tp-e ( $R=-0.34$ ,  $P<0.01$ ). There was no significant correlation between Tp-e and whole heart DOR with norepinephrine infusion at 1 minute ( $R=0.36$ ,  $P=0.25$ ) or 2 minutes ( $R=0.41$ ,  $P=0.17$ ).

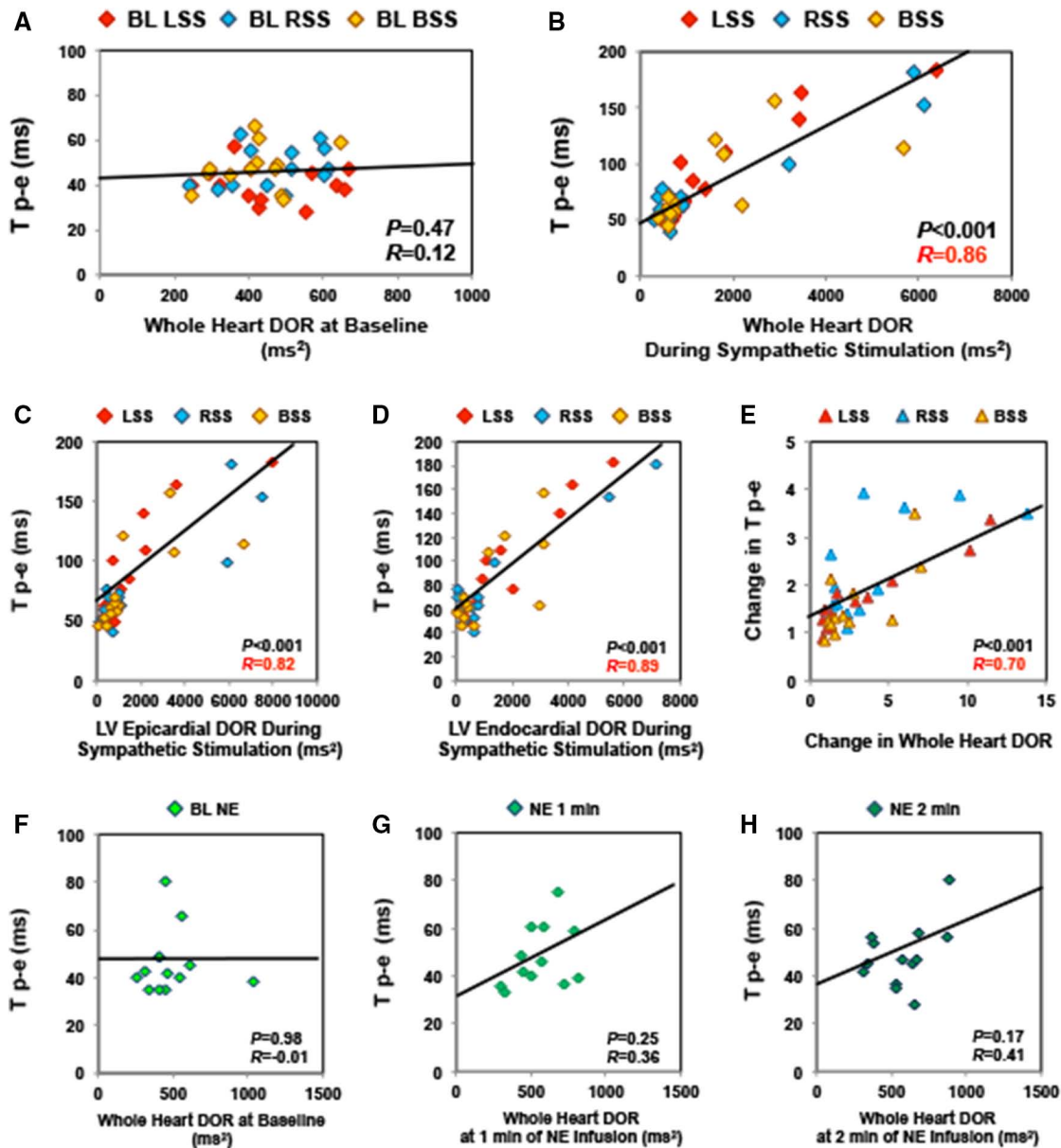
**Discussion**

**Major Findings**

The major findings of this study are (1) sympathetic nerve stimulation increased Tp-e and whole heart DOR, whereas norepinephrine infusion had no effect on Tp-e or DOR; (2) Tp-e was strongly correlated with DOR of the epicardium and endocardium during sympathetic nerve activation; and (3) the regional functional innervation patterns of the LV endocardium were similar to that of the LV epicardium during LSS, RSS, and BSS.

**Increase in DOR by Sympathetic Nerve Stimulation Is Reflected in the Increase in Tp-e**

Tp-e is a strong predictor of the risk of sudden cardiac death in patients with congenital channelopathies and structural heart disease.<sup>7-12</sup> In cardiac wedge preparation studies, Tp-e was reported to reflect TDR.<sup>7,14,15</sup> However, more recently, Tp-e has been reported to correlate with whole heart DOR. Opthof et al.<sup>17</sup> investigated epicardial, endocardial, and mid myocardial recovery times in a canine LV and found no correlation between Tp-e and transmural DOR; however, Tp-e was correlated with DOR of the whole heart. Izumi et al.<sup>16</sup> found that the Tp-e reflects spatial DOR rather than TDR in a drug-induced long QT model. Yet, effects of sympathetic activation, and specifically, stimulation of the nerves versus circulating catecholamines on Tp-e have been less clear. Our group recently reported that the change in epicardial dispersion of RT by LSS and RSS correlated with Tp-e. The results of the current



**Figure 8.** T-peak to T-end interval (Tp-e) does not correlate with dispersion of repolarization (DOR) at baseline before sympathetic nerve stimulation (A). However, it strongly correlates with the DOR of the entire left ventricular (LV) and right ventricular epicardium and LV endocardium during stellate ganglia (SG) stimulation (B). Correlation with LV epicardial DOR (C) and LV endocardial DOR (D) during SG stimulation is shown. The change in Tp-e was strongly correlated with the change in whole heart DOR (E). Tp-e did not significantly correlate with DOR at baseline before norepinephrine infusion (NE) infusion (F) or at 1 and 2 minutes after NE infusion (G,H). For comparison of the correlation between Tp-e and DOR, Pearson product-moment correlation coefficient was used. BL indicates baseline; BSS, bilateral stellate stimulation; LSS, left stellate stimulation; and RSS, right stellate stimulation.

study takes these findings a step further in showing that the pattern of endocardial DOR caused by sympathetic activation followed that of the epicardium, that BSS can also increase DOR and Tp-e, and that norepinephrine does not significantly affect DOR or Tp-e. Furthermore, increase in DOR with LSS, RSS, and BSS occurred despite tachycardia, which can mitigate DOR.<sup>23</sup> LSS had the strongest effect on Tp-e and DOR. Sympathetic stimulation, particularly LSS, is also known to increase risk of ventricular arrhythmias, early after depolarizations, and delayed after depolarization.<sup>24–26</sup> Therefore, our results suggest that the increase in Tp-e may be a reflection of increased sympathetic nerve activation, which can lead to sudden cardiac death.

Importantly, norepinephrine infusion did not significantly increase DOR, ARI variance, or Tp-e in the ventricles. Tanabe et al<sup>8</sup> found that epinephrine increased Tp-e as an index of DOR in patients with long QT syndrome but not healthy control patients. The increase in DOR by epinephrine in long QT syndrome patients may be caused by heterogeneous distribution of Ca<sup>2+</sup>-activated  $I_{Ks}$ ,  $I_{Cl}$ , or  $I_{Na-Ca}$  channels.<sup>27</sup> In this porcine model, the increases in DOR seem to be a function of sympathetic innervation rather than distribution of beta receptors or  $I_{Ks}$  channels. Circulating catecholamines uniformly affect beta adrenergic receptors throughout the ventricles, resulting in little change in DOR or Tp-e.

## Electrophysiological Effects of Sympathetic Stimulation on LV Epicardium Versus Endocardium

Yanowitz et al<sup>28</sup> in 1966 demonstrated that right stellectomy led to refractory period prolongation on the LV anterior wall, and left stellectomy prolonged refractory periods on the posterior wall. However, their assessment was limited to LV anterior and posterior walls. Opthof et al<sup>29</sup> demonstrated shortening of ventricular fibrillation intervals on the posterior and lateral epicardial walls of the ventricles during LSS, whereas RSS shortened ventricular fibrillation intervals on the anterior epicardial wall. Our study shows that functional sympathetic innervation of the LV endocardium follows that of the LV epicardium. No regional differences were found during BSS. ARI shortening was greater on the posterior and lateral LV endocardium during LSS, whereas RSS decreased endocardial ARI more on the anterior and lateral endocardial walls. LV endocardial lateral wall was an area of overlap between the 2 stellates. The LV endocardial ARI on the septum significantly shortened during LSS compared with the anterior wall, whereas there was no significant endocardial ARI shortening on the septum compared with the anterior wall or posterior wall during RSS. Therefore, LV endocardial septum may be a territory of greater left sympathetic nerve innervation.

Cardiac sympathetic denervation therapy has been used as a treatment option for patients with ventricular arrhythmias refractory to medical therapy and catheter ablation.<sup>5,6</sup> Which patients will benefit from left, right, or bilateral cervicothoracic sympathectomy and underlying mechanisms of benefit remain unclear. This study supports the hypothesis that the decrease in heterogeneity of refractoriness or DOR caused by sympathetic activation may serve as one potential mechanism behind the benefits of this procedure.

It is thought that as a result of its embryological development, sympathetic fibers may be more densely distributed on the subepicardium with denervation of the epicardium disrupting response to sympathetic stimulation.<sup>30</sup> However, in this study, no significant change in ARI or RT of the LV endocardium versus epicardium during sympathetic stimulation was found. Martins et al reported similar findings by demonstrating no change in epicardial and endocardial refractory periods before and after sympathetic stimulation.<sup>31</sup> Of note, in this study, the ARI was shorter on the endocardium than epicardium at baseline, consistent with other reports of refractory periods measured in a porcine ventricle.<sup>32,33</sup>

### Limitations

Electrogram recordings on the RV endocardium and from the mid myocardial layer (M-cell layer) were not obtained in this study. In addition, general anesthesia with inhaled isoflurane can suppress nerve activity. In this study, anesthesia was switched from isoflurane to  $\alpha$ -chloralose after surgical preparation to reduce anesthetic effects. Furthermore, a strong hemodynamic and electrophysiological response to stimulation was observed. ARI and Tp-e during each stimulation were not corrected for HR. RSS and BSS but not LSS increased HR. However, regional ARIs and RTs, TDR, and correlation of RT with Tp-e were compared at similar HR (at baseline or

during intervention). In addition, any HR effects on DOR are of physiological importance. The stimulation and norepinephrine infusion protocols in this study were fixed. Therefore, it is possible that an intervention could have effects on subsequent interventions. However, after the 20 minute waiting period, all parameters, including ARI, ECG, and hemodynamic values, had returned to baseline levels before performance of additional stimulation/infusion, and the values for each intervention were compared with the prestimulation/infusion value just before the start of that intervention. In this study, we chose to infuse norepinephrine at 0.3  $\mu\text{g}/\text{kg}/\text{min}$ , and it is possible that this dose may not be sufficient to raise myocardial norepinephrine levels to those comparable to nerve stimulation. However, this dose is 3 times the dose used in advanced cardiac life support protocol or septic shock.<sup>34,35</sup> Therefore, we chose a relatively high dose to achieve a hemodynamic response similar to that achieved by nerve stimulation.

### Conclusions

Tp-e is modulated by left, right, and bilateral SG stimulation, but not by circulating norepinephrine. Therefore, increases in Tp-e are a reflection of increased sympathetic nerve activity, rather than release of circulating norepinephrine. Effects of SG stimulation on regional innervation patterns of the LV endocardium are similar to that of the LV epicardium. The reduction in DOR and heterogeneity of repolarization as a result of the functional distribution of sympathetic innervation may serve as one mechanism behind the therapeutic benefits of cervicothoracic sympathectomy.

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### Disclosures

The University of California, Los Angeles, has intellectual property developed by one of the authors (K. Shivkumar) that relate to epicardial interventions.

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## Sympathetic Nerve Stimulation, Not Circulating Norepinephrine, Modulates T-Peak to T-End Interval by Increasing Global Dispersion of Repolarization

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