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Minimally Invasive Transtracheal Cardiac Plexus Block for Sympathetic Neuromodulation

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Abstract

Background: Bilateral thoracoscopic stellectomy has antiarrhythmic effects, however, the procedure is invasive with associated morbidity. Sympathetic nerves from both stellate ganglia form the deep cardiac plexus (CP) in the aortopulmonary window (APW), anterior to the trachea.

Objective: To demonstrate a novel and minimally invasive transtracheal approach to block the cardiac plexus in porcine models.

Methods: In 12 Yorkshire pigs, right (RSG) and left (LSG) stellate ganglia were electrically stimulated and sympathetic baseline response recorded (hemodynamic parameters and T wave pattern). APW was accessed transtracheally with endobronchial ultrasound (EBUS) guidance and local stimulation of CP confirmed the location. Injection of 1% lidocaine (n=10) or saline solution (n=2) was performed and RSG and LSG responses were re-evaluated and compared with baseline.

Results: Transtracheal lidocaine injection into the CP successfully blocked bilateral sympathetic induced changes (%) in T wave amplitude (282.8 ± 152.2 vs $20.1 \pm 16.5\%$, $p < 0.001$ [LSG]); 338.9 ± 189.8 vs $28 \pm 18.3\%$, $p < 0.001$ [RSG]), Tp-Te interval (87.9 ± 37.2 vs $6.9 \pm 6.7\%$, $p < 0.001$ [LSG]); 32.6 ± 27.4 vs $6.9 \pm 4.7\%$, $p < 0.035$ [RSG]) and left ventricular dP/dT_{max} (148.3 ± 108.5 vs $16.5 \pm 13.4\%$, $p < 0.001$ [LSG]; 243.1 ± 105.2 vs $19.0 \pm 12.4\%$, $p < 0.001$ [RSG]). RSG induced elevation of systemic, left ventricular and pulmonary arterial pressures were blocked by

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lidocaine injection into CP ($p < 0.005$ for all comparisons). Stellate ganglia response was not affected in sham studies. No complications were observed during the procedures.

Conclusion: Minimally invasive transtracheal injection of lidocaine into the CP blocked the sympathetic response of either RSG and LSG. Transtracheal assessment of CP may allow for minimally invasive and selective ablation of cardiac innervation, extending the CSD benefits to those not suitable for surgery.

Graphical Abstract

Keywords

cardiac plexus; sympathectomy; denervation; transtracheal; EBUS; ventricular tachycardia; refractory arrhythmia; stellate ganglia; aortopulmonary window; neuromodulation

Introduction

Despite advances in management of ventricular arrhythmias, ventricular tachycardia (VT) recurrence is not uncommon after ablation and is associated with significant morbidity and mortality^{1, 2}. The role of the autonomic nervous system in genesis and perpetuation of arrhythmias is now well recognized and cardiac neuromodulation has emerged as a therapeutic modality, especially in patients with refractory arrhythmias.^{3–5} Recently, bilateral cardiac sympathectomy denervation (BCSD) has gained importance as a fair alternative in refractory cases.⁶ However, the procedure of BCSD involves thoracoscopic surgical resection of stellate ganglia and proximal thoracic ganglia bilaterally, under single lung ventilation, which is not tolerated by many patients with cardiopulmonary disease. Furthermore, BCSD has a host of off target effects related to the surgery such as lung injury, compensatory hyperhidrosis and Horner's syndrome. As such, there is an enormous need for a minimally invasive technique to achieve selective bilateral sympathetic denervation/blockade in patients with refractory arrhythmias.

Sympathetic nerves from both stellate ganglia (SG) converge to form the deep cardiac plexus (CP), a complex network of nerves traveling along a confined space between the pulmonary artery, aortic arch, and anterior wall of the trachea (aortopulmonary window –APW).⁷ Catheter stimulation of cardiac nerves and its physiological effects have been previously reported in canine models.⁸ However, by virtue of its complexity and anatomic restrictions, direct stimulation or local blockade/ denervation of cardiac plexus has been poorly explored.

In this study, we describe a novel, minimally invasive, transtracheal approach to access, stimulate, and block the cardiac sympathetic inputs distally and bilaterally from a single site.

Methods

Study design

Twelve female Yorkshire pigs were subjected to minimally invasive transtracheal access to deep CP through the APW, using endobronchial ultrasound (EBUS) guidance. Bilateral stellate ganglia (SG) sympathetic responses were evaluated before and after transtracheal injection of lidocaine (n=10) or saline solution (n=2) in order to explore feasibility and effects of transient blockade of CP.

All animal studies were approved by Johns Hopkins University Animal Care and Use Committee.

Animal preparation—Twelve female Yorkshire pigs (30–35kg) were placed under general anesthesia with inhaled isoflurane 0.5–1.5% and 100% O₂ support. Appropriate vascular femoral accesses were established, and a saline solution was infused throughout the procedure (500–1000ml). A 6F sheath was placed in left carotid artery for left ventricular (LV) pressure catheter positioning. Multiparametric monitoring was performed.

ECG and hemodynamic recording—ECG, heart rate (HR), systolic systemic blood pressure (SBP_{syst}), systolic pulmonary artery pressure (PAP_{syst}), end-systolic left ventricular pressure (LVP_{endsyst}) and maximum left ventricular dP/dT (LV dP/dT_{max}) were monitored and recorded during the entire procedure. A 5F Mikro-tip pressure catheter (Millar Instruments Inc, Houston, TX, USA) was positioned in LV and LVP_{endsyst} and dP/dT_{max} were recorded using dedicated pressure control unit (PCU-2000, Millar Instruments Inc, Houston, TX, USA). Data points were extracted over a 15 second time window immediately before and after ganglia stimulation. Data acquisition was performed by PowerLab and digital processing by LabChart Pro 8 (ADInstruments, NSW, Australia). Values were obtained during baseline and after stellate stimulation, before and after deep CP injection (lidocaine or saline solution), and compared as detailed in the following sections. By virtue of disparity in baseline values, mean absolute variation ([post-stimulation value – baseline value]/ baseline; %) of variables were used to compare changes in sympathetic response before and after transtracheal injection. T wave amplitude and T peak to end (Tp-Te) interval responses for both RSGS and LSGS were obtained after the procedure and compared with baseline as previously described.⁹

Sympathetic block was primarily confirmed by inhibition of T wave pattern modifications (lead aVF) and mitigation of LV dP/dT_{max} incremental response upon either right stellate ganglion (RSG) and left stellate ganglion (LSG) stimulation. RSG and LSG were re-stimulated two hours after lidocaine block and sympathetic response was re-assessed.

Stellate ganglion stimulation—Two 10-mm tip quadripolar ablation catheters (Blazer II, Boston Scientific, Marlborough, MA, USA) were intravascularly positioned into right and left subclavian arteries, adjacent to RSG and LSG, using transaortic retrograde access as previously reported (Figure 1, supplemental material).¹⁰ Animals were randomly assigned to first receive RSG or LSG stimulation. High voltage bipolar stimulation (30–60mA, 0.01s, 20Hz, for 10–15s) was sequentially applied onto stellate ganglia in order to generate a typical and consistent baseline sympathetic heart response from each ganglion (A385RC stimulator, World Precision Instruments, Sarasota, FL, USA). At RSG stimulation (RSGS), a minimum 25% increase in LV dP/dT_{max} and T wave inversion were required for assuming an adequate response; at LSG stimulation (LSGS), an adequate response was considered when a minimum 25% increase in LV dP/dT_{max} was accompanied by a minimum 50% increase in T wave amplitude. A 20–30-minute interval was employed between ganglia stimulations. The stimulation catheters were kept in the same position during the entire study. RSG and LSG sympathetic responses were re-evaluated after the procedure (Transtacheal approach section) by repeating the stimulation protocol.

Transtacheal approach (endobronchial ultrasound guided – EBUS)—All subjects underwent EBUS guided 22-gauge transtacheal needle injections in the APW. EBUS bronchoscope was introduced through the endotracheal tube, without interruption of ventilatory support. EBUS was performed using a built in curvilinear 7.5 MHz convex array ultrasound transducer with Doppler capabilities (50mm penetration), with an outer diameter of 6.9 mm and 30° oblique forward viewing optics (BF-UC180F, Olympus, Tokyo, Japan). A custom, specially designed prototype echogenic needle with unipolar electrodes was inserted through the 2.2mm working channel to access the APW through the anterior wall of the trachea (Figure 1). EBUS real time imaging of pre-tracheal space defined puncture sites. Manipulation of the needle in the pre-tracheal space was continuously monitored by EBUS to avoid vascular and lung injuries. CP location was confirmed by induction of left or right stellate ganglia sympathetic response-like by unipolar needle electrical stimulation (10–20mA, 0.01s, 20Hz, for 10–15 seconds). After electrical confirmation, contrast was injected to reassure soft tissue staining without run off and to avoid inadvertent injection into either the vessel or pericardial space.

In the study group, ten animals underwent injection of 1% lidocaine in the APW and eventually in the lower right para-tracheal space (RPS). Animals which demonstrated complete block of LSG response but partial block of RSG response after lidocaine injection in the APW, received one additional injection in the lower RPS. In the sham group, two animals underwent injection of saline solution (2 injections; 4ml/ injection) into the APW and in the lower RPS. All animals underwent terminal studies and were euthanized and submitted to a detailed open-chest visual inspection for collateral damage.

Statistical analysis—Continuous variables are expressed as mean $\pm$ standard deviation (SD) and compared across groups using Mann–Whitney U-test. To account for baseline differences, the change/ variation in variables was also compared and defined as the difference between stimulation and baseline values divided by the baseline value (%). A P-value <0.05 was considered significant. SPSS Version 24 (IBM, Chicago, IL, USA) was used for all statistical analysis.

Results

Direct Stellate Ganglia Stimulation and Sympathetic Response

Stellate ganglion stimulation consistently elicited characteristic response in all animals similar to prior published studies.^{10–13}

At rest (before lidocaine injection), increase in mean LV dP/dT_{max} (1294.5 ± 430.7 mmHg/s [Baseline]; 2852.0 ± 569.3 mmHg/s [LSGS]; 4146.4 ± 997.4 mmHg/s [RSGS]), changes in T wave pattern and amplitude (0.17 ± 0.06 mV [Baseline], 0.62 ± 0.17 mV [LSGS], -0.36 ± 0.2 mV [RSGS]) and prolongation of Tp-Te interval (35.9 ± 4.3 ms [Baseline], 67.2 ± 13.6 ms [LSGS], 46.9 ± 8.9 ms [RSGS]), by either RSGS or LSGS, were observed in all animals ($p < 0.005$ for all comparisons) (Table 1). Tp-Te interval prolongation was more pronounced under LSGS when compared to RSGS.

RSGS also consistently induced an increase in SBP_{syst} (106.2 ± 7.8 to 128.4 ± 9.2 mmHg), LVP_{endsyst} (94.5 ± 7.7 to 114.7 ± 7.5 mmHg), PAP_{syst} (30.5 ± 5.0 to 45.0 ± 8.4 mmHg) and HR (88.1 ± 15.6 to 137.7 ± 14.1 bpm) when compared with baseline ($p < 0.001$ for all comparisons). Frequent ventricular arrhythmias including runs of ventricular tachycardia were noted during LSGS in 6/12 subjects (50%). One ventricular fibrillation episode was induced by LSGS.

EBUS guided needle stimulation in different sites along the APW elicited different sympathetic responses, ranging from predominantly LSGS-like response (T wave elevation associated with an increase in LV dP/dT_{max}) over the left side of APW, to predominantly RSGS-like response (T wave inversion associated with an increase in HR, BP and/or LV dP/dT_{max}) towards the right side of the APW, and showed similar magnitude compared to percutaneous stimulation (Figure 2, supplemental material).

Lidocaine Block of Deep Cardiac Plexus

In study group, EBUS-guided 1% lidocaine injection in CP (6–10ml; 2ml per injection) resulted in effective block of RSG and LSG responses (Figure 2 and 3). Out of the 10 test animals, four required one additional injection of 1% lidocaine in lower right para-tracheal space (RPS) above the right pulmonary artery (2ml) to obtain complete RSG block (Figure 1B, **red circle**).

Two hours after lidocaine injection, we were able to re-provoke the RSG and LSG responses, confirming reversibility of sympathetic block (Figure 4A). All subjects in sham group received injections in APW and RPS in order to accurately reproduce the study group procedure. Sympathetic responses were not affected in sham group subjects after the

procedure (Figure 4B). No vascular injuries occurred. Neither acute complications during the procedure nor collateral damage upon open-chest inspection was observed in both groups.

Lidocaine injection into the APW generated a slight elevation of T wave amplitude (0.17 ± 0.06 to 0.28 ± 0.05 mV, $p=0.001$) and associated Tp-Te interval prolongation (35.9 ± 4.3 to 46.2 ± 12.2 ms, $p<0.043$) in all subjects in study group when compared to baseline. Such pattern was also identified in some subjects even before injection (manipulation of the needle into the CP). Lidocaine CP block also reduced baseline SBP_{syst} and $LVP_{endsyst}$, however neither hemodynamic instability nor vasoactive drug requirement was observed along the studies. Baseline hemodynamic parameters was not influenced by saline injection in sham group.

Deep Cardiac Plexus Block and Right Stellate Ganglion Stimulation Response

EBUS-guided transtracheal injection of lidocaine in the CP resulted in marked inhibition of all evaluated RSG sympathetic responses. As shown in Figure 5, after lidocaine injection, changes in $LV\ dP/dT_{max}$ (243.1 ± 105.2 to $19.0 \pm 12.4\%$), SBP_{syst} (21.5 ± 12.6 to $7.0 \pm 5.1\%$), $LVP_{endsyst}$ (22.0 ± 11.3 to $7.6 \pm 5.7\%$), PAP_{syst} (49.3 ± 27.7 to $6.2 \pm 6.3\%$) and HR (60.1 ± 27.8 to $6.4 \pm 6.8\%$) were significantly reduced when compared with baseline response ($p<0.005$ for all comparisons). Typical evoked T wave inversion presented at baseline stimulation was completely abolished in all animals in study group, wherein changes on T wave amplitude (338.9 ± 189.8 to $28.0 \pm 18.3\%$, $p<0.001$) and Tp-Te interval (32.6 ± 27.4 to $6.9 \pm 4.7\%$, $p<0.035$) were mitigated after lidocaine block of CP.

Deep Cardiac Plexus Block and Left Stellate Ganglion Stimulation Response

EBUS guided transtracheal injection of lidocaine in CP also blocked incremental response of $LV\ dP/dT_{max}$ induced by LSGS (148.3 ± 108.5 to $16.5 \pm 13.4\%$; $p<0.001$). Deep CP block eliminated LSGS induced peaked T wave pattern as a result of inhibited incremental responses of T wave amplitude (282.8 ± 152.2 to $20.1 \pm 16.5\%$; $p<0.001$) and Tp-Te interval (87.9 ± 37.2 to $6.9 \pm 6.7\%$; $p<0.001$) (Figure 5).

Discussion

In this report, we exploited the unique anatomy of the cardiac sympathetic nerves and devised a novel minimally invasive transtracheal approach to block cardiac sympathetic plexus in the APW. Cardiac sympathetic nerves from both sides can be accessed through this approach at a single site and successfully blocked to assess their impact on ventricular arrhythmias. This might help to best select appropriate patients for BCSD and, with development of appropriate ablation tools, may allow for minimally invasive inactivation of CP, obviating the need of surgery to treat refractory ventricular dysrhythmias.

Surgical sympathetic denervation has proven to be effective in reducing arrhythmic burden in patients with refractory VT. Patients with Long-QT Syndrome and Catecholaminergic Polymorphic VT had benefited from surgical sympatholysis, which has also led to improved arrhythmic outcomes and reduced ICD shocks in patients with both ischemic and non-ischemic structural heart disease.^{6, 14, 15} Transient sympathetic block seems to be effective in

achieving acute control of electrical storm¹⁶, as provided by thoracic epidural anesthesia (TEA) or stellate ganglion anesthetic blockade (SGAB). TEA is contraindicated in patients on anticoagulants. Bilateral SGAB is not performed clinically due to risk of bilateral laryngeal and/or phrenic palsy¹⁷. Neither TEA or SGAB can predict BCSD outcome.

BCSD, at best, results in debulking of the cardiac sympathetic inputs, as it is well recognized that the cardiac nerves also arise from the middle cervical ganglion, which are largely unaffected by the surgical procedure.¹⁸ On the contrary, the transtracheal approach employs accessing and targeting the cardiac nerves distally, as they enter the pericardium, resulting in a broader and complete sympathetic block.

Vagus nerve runs posterior to the trachea and the vagal inputs to the heart join the ventrolateral cardiac nerve which run anterior and lateral to the arch of the aorta and hence is unlikely to be affected by the transtracheal approach. At no point during our electrical stimulation in the deep CP region we encountered vagal responses such as bradycardia or hypotension. All responses recorded were consistent with sympathetic stimulation and were similar to the responses elicited by SG stimulation. Thus, we believe that interventions limited to the APW will result in predominant sympathetic blockade which is desirable in cardiovascular pathologic conditions.

The anatomy of the extra-cardiac nerves and of the deep cardiac plexus in humans is well published⁷ and appears to be similar to the anatomic location of the deep plexus of porcine subjects in the APW. The location of the plexus in front of the tracheal bifurcation, behind the aorta and the pulmonary bifurcation, makes our transtracheal approach an easy access to the otherwise forbidden space. Other researchers have attempted to denervate parts of the deep CP through the pulmonary artery to treat pulmonary hypertension.¹⁹ Despite several attempts we could not electrically stimulate the plexus through the pulmonary artery. We believe that the cardiac plexus lies posterior to the great vessels and closer to the trachea making ablation through the intravascular space challenging and with significant risk for vascular injury at the cost of poor denervation.

EBUS was used to access the APW in our study. This technique was devised based on the anatomical constraints of the APW and adds to the novelty of this study. EBUS is routinely performed by pulmonary physicians and EBUS-guided interventions are safe and currently applied in standard of care for real-time visualization during needle assessment of mediastinal structures adjacent to the airway.²⁰ Thereby, we did not observe vascular or surrounding structures damage during transtracheal assessment of APW, which stands for the safety profile of the technique.

Clinical implications

Elevated central sympathetic tone is uniformly associated with a poor prognosis in all forms of structural heart disease.²¹ Beta-blocker agents, by blocking the sympathetic response, improve survival in various cardiovascular disorders and are the cornerstone for management of coronary disease, heart failure and cardiac arrhythmias.^{22–24} Lack of stellate ganglia sympathetic response after lidocaine injection in APW may act as a surrogate for BCSD. Additionally, prior reports have addressed the relationship between Tp-Te interval

and dispersion of repolarization associated with sympathetic driven states¹², and its value in risk prediction models for arrhythmias and sudden cardiac death.^{9, 25} Lidocaine block of CP successfully inhibited prolongation of Tp-Te interval corroborating the anti-arrhythmic properties of transtracheal block of CP.

Further, deep cardiac nerves may be permanently disabled via EBUS-guided minimally invasive approach either chemically, or via ablative techniques, to achieve selective and near complete sympathetic denervation of the heart to treat cardiovascular disorders. Distal sympatholysis may also avoid the complications of BCSD such as hyperhidrosis of the lower half of the body, Horner's syndrome, and pulmonary complications. Patients who are poor surgical candidates and those with pulmonary comorbidities who would otherwise be unsuitable for BCSD may be candidates for transtracheal sympatholysis.

Study limitations

It is possible that the lidocaine crossed facial planes and led to block in regions remote to the APW, however, contrast injection in all cases confirmed local and restricted soft tissue staining (APW). Additionally, the injection could be visualized on the ultrasound with the tip of the needle wedged in the soft tissue of the APW, thus avoiding intravascular injection. As such we are confident that the effect was localized. Baseline RSGS and LSGS responses were re-provoked two hours after the procedure (lidocaine washout), which favors functional block over anatomic disruption due to needle insertion.

In our study, elimination of characteristic stellate response from both ganglia was demonstrated as a result of local cardiac plexus block, however, whether it shares the same antiarrhythmic effects derived from BCSD was not specifically addressed. Additionally, this study did not address the effects of permanent denervation of cardiac plexus and the risks associated with this novel transtracheal approach. As such, the long-term safety profile of transtracheal approach needs to be explored in detail before considering this as an alternative to a well-established procedure.

Conclusion

Our study proposes a novel, minimally invasive and more selective cardiac neuromodulation technique by demonstrating the feasibility and efficacy of EBUS-guided transtracheal transient denervation of cardiac plexus in animal models. We believe that transtracheal assessment for sympathetic neuromodulation carries a potential role not only as a safe transient surrogate for surgical sympathectomy, enabling its use in response prediction models, but also as a minimally invasive treatment modality for acute management of refractory tachyarrhythmias. Furthermore, transtracheal assessment of CP may allow for minimally invasive and selective ablation of cardiac innervation, extending the CSD benefits to those not suitable for surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

EBUS-guided transtracheal blockade of cardiac plexus. (A) Ultrasound real-time imaging of the aortopulmonary (AP) window allows for safe positioning of injection needle into the pre-tracheal space (illustration). (B) EBUS needle is advanced through the trachea anterior wall into the space between the aortic arch and pulmonary artery. Injection of a contrast-lidocaine solution into the site of block (AP window) demonstrates the absence of either systemic (intravascular) or intrapericardial inadvertent assessment (lower right). Stellate ganglia stimulation catheters are shown in the background. AO= aorta (arch). EBUS= endobronchial ultrasound. PA= pulmonary artery. (PA)= posteroanterior projection. (RAO)= right anterior oblique projection. Red circle= right para-tracheal space (see text for further details).

Figure 2.

Effects of cardiac plexus blockade on stellate hemodynamic sympathetic response. On each graphic, LVP is represented at baseline and after stellate ganglia stimulation (RSGS and LSGS). After lidocaine injection (on the right), baseline incremental sympathetic changes on LVP induced by either RSGS and LSGS were abolished, which was accompanied by elimination of LV dp/dt sympathetic response. LVP= left ventricular pressure. LV dp/dt = rate of left ventricle pressure change. LSGS= left stellate ganglion stimulation. RSGS= right stellate ganglion stimulation. SG= stellate ganglion.

Figure 3.

Effects of cardiac plexus blockade on stellate T wave sympathetic response. (A) T wave amplitude sympathetic changes induced by RSGS and LSGS were significantly inhibited by lidocaine, bilaterally. (B) T wave pattern modifications induced by RSGS (T wave inversion) and LSGS (T wave elevation) were eliminated by lidocaine cardiac plexus block (lead aVF). LSGS= left stellate ganglion stimulation. RSGS= right stellate ganglion stimulation.

Figure 4.

Cardiac plexus blockade recovery and effects of sham injection on sympathetic response. (A) Transient bilateral sympathetic block was followed by full recovery after lidocaine washout (subject 9). (B) T wave amplitude and LV dP/dT sympathetic responses were not affected by saline injection into the cardiac plexus. Abbreviations see Table 1.

Figure 5.

Absolute changes (%) in stellate ganglia sympathetic responses at baseline (before lidocaine injection), at lidocaine blockade of cardiac plexus, and after lidocaine washout (recovery). After lidocaine injection, all RSGS induced sympathetic changes were mitigated when compared with baseline response. For LSGS, sympathetic changes which were significantly present at baseline were blocked by lidocaine injection. At recovery, bilateral sympathetic response was reestablished. Values are given by mean $\pm$ SD. Abbreviations see Table 1.

Table 1. Stellate ganglia sympathetic response before and after lidocaine blockade of cardiac plexus

Before lidocaine injection, a significant elevation in LV dP/dT_{max} and change in T wave features (amplitude and Tp-Te interval) were induced by both RSGS and LSGS ($p < 0.005$), with an incremental response for all monitored pressures under RSGS ($p < 0.001$). Lidocaine injection into deep CP successfully inhibited all induced sympathetic responses, bilaterally (see text for further details). A reduction of baseline values of SBP_{syst} and LVP_{endsyst} was observed after lidocaine injection, as well as a slight increase in T wave amplitude and Tp-Te interval. Values are given by mean $\pm$ SD. HR= heart rate. LV dP/dT_{max}= maximum rate of change in left ventricular pressure. LVP_{endsyst}= end-systolic left ventricular pressure. LSGS= left stellate ganglion stimulation. PAP_{syst}= systolic pulmonary arterial pressure. RSGS= right stellate ganglion stimulation. SBP_{syst}= systolic systemic blood pressure. Tp-Te interval= T peak to T end interval.

	Before lidocaine				After lidocaine			
	Baseline 1	RSGS	P value [†]	LSGS	P value [†]	Baseline 2	RSGS	P value [‡]
SBP _{syst} (mmHg)	106.2 $\pm$ 7.8	128.4 $\pm$ 9.2	<0.001	112.0 $\pm$ 15.3	0.529	90.2 $\pm$ 8.3 [§]	88.7 $\pm$ 10.3	0.684
LVP _{endsyst} (mmHg)	94.5 $\pm$ 7.7	114.7 $\pm$ 7.5	<0.001	102.1 $\pm$ 12.3	0.105	80.6 $\pm$ 7.3 [§]	79.8 $\pm$ 9.4	0.481
PAP _{syst} (mmHg)	30.5 $\pm$ 5.0	45.0 $\pm$ 8.4	<0.001	36.2 $\pm$ 3.2	0.579	29.3 $\pm$ 3.3	29.8 $\pm$ 3.0	0.853
HR (bpm)	88.1 $\pm$ 15.6	137.7 $\pm$ 14.1	<0.001	90.2 $\pm$ 15.1	0.019	82.1 $\pm$ 9.5	85.3 $\pm$ 15.1	0.912
LV dP/dT _{max} (mmHg/s)	1294.5 $\pm$ 430.7	4146.4 $\pm$ 997.4	<0.001	2852.0 $\pm$ 569.3	<0.001	1240.8 $\pm$ 154.6	1318.4 $\pm$ 381.5	0.853
T wave amplitude (mV)	0.17 $\pm$ 0.06	-0.36 $\pm$ 0.20	<0.001	0.62 $\pm$ 0.17	<0.001	0.28 $\pm$ 0.05 [§]	0.29 $\pm$ 0.08	0.971
Tp-Te interval (ms)	35.9 $\pm$ 4.3	46.9 $\pm$ 8.9	0.004	67.2 $\pm$ 13.6	<0.001	46.2 $\pm$ 12.2 [§]	48.7 $\pm$ 14.1	0.853

[†] compared to values at baseline 1.

[‡] compared to values at baseline 2.

[§] significant difference compared to values at baseline 1 ($p < 0.05$).