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A new electrocardiographic marker for sympathetic nerve stimulation: modulation of repolarization by stimulation of stellate ganglia☆

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Abstract Activation of cardiac sympathetic nerves alters ventricular repolarization; however, these changes remain poorly characterized. The goal of this study was to examine effects of sympathetic stimulation on repolarization to identify electrocardiographic markers of sympathetic activation. Pigs underwent median sternotomy and bilateral thoracotomy to expose the stellate ganglia. Changes in T-wave duration, amplitude, repolarization vector, and time from peak to end (Tp-Te) were continuously monitored. Within 15 seconds of unilateral left or right stellate ganglion (LSG/RSG) stimulation, T-wave amplitude increased 6- and 4.5-fold, respectively, in lead aVF. T-wave duration and Tp-Te both increased 200% during LSG stimulation but only 50% and 30%, respectively, with RSG stimulation. During LSG stimulation, frontal and horizontal T-wave vectors, respectively, changed from 1.9° ± 22.8° and 333.8° ± 9.7° at baseline to 83.4° ± 3.9° (inferiorly) and 306.7° ± 1.8° (posteriorly). During RSG stimulation, frontal and horizontal T-wave vectors changed from 348.2° ± 21.6° and 333.8° ± 10.3° before stimulation to 280.7° ± 4.6° (superiorly) and 118.1° ± 5.6° (anteriorly). During stellate stimulation, T-wave vectors are displaced to angles specific for LSG activation (posteroinferiorly) or RSG activation (anterosuperiorly); T-wave amplitude, duration, and Tp-Te increase; and ST-duration decreases. Displaced repolarization vector and changes in T-wave morphometrics provide a novel marker of unilateral sympathetic nerve stimulation.

Keywords: Sympathetic nerve stimulation; Ventricular repolarization vector; Electrocardiography; Stellate ganglia

Introduction

Myocardial function is regulated by the sympathetic and parasympathetic components of the autonomic nervous system[1] that affect inotropy and chronotropy[2] as well as myocardial repolarization.[3] Ventricular repolarization is represented electrocardiographically by the T-wave, with the net T-wave vector arising from regional differences in repolarization timing (epicardium to endocardium, apex to base).[4] Regional alterations in ventricular repolarization can play a critical role in arrhythmia initiation and maintenance, whereby differences in repolarization timing between adjacent areas can facilitate conduction slowing or unidirectional block. Changes in repolarization can be detected by changes in T-wave properties such as onset, width, or amplitude. Autonomic activation of the left and right stellate ganglia (LSG and RSG, respectively) is one mechanism that can alter ventricular repolarization[5,6] evidenced by changes T-wave amplitude and vector loops.[7] Although alterations in ventricular repolarization play a critical role in arrhythmia initiation and maintenance, there remains a gap between the supporting experimental evidence[8] and clinical tools for stratification and treatment for patients with existing substrates that predispose to arrhythmias. The electrocardiogram (ECG) is a widespread tool that may provide further insights into diagnosis or stratification of arrhythmias based on changes in ventricular repolarization.

The purpose of this study was to examine the effects of postganglionic sympathetic stimulation on morphometrics of ventricular repolarization during unilateral LSG or RSG stimulation, as evidenced by the surface ECG. The clinical

☆ Conflicts of Interest for all authors: none.

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potential for noninvasive markers such as morphometric T-wave changes as potential indicators of sympathetic surge in humans could have important implications for identifying patients for whom neuraxial modification would be an effective treatment of for arrhythmias refractory to medical and catheter-based ablative therapies.

Methods

Surgical preparation

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

Anesthetized female Yorkshire pigs weighing 25 to 40 kg underwent median sternotomy and bilateral thoracotomy to expose the anterior surface of the heart and sympathetic nerves of the posterior thorax. Animals were medicated with intramuscular telazol (8-10 mg/kg) and fentanyl (50-100 μg) then intubated and ventilated after administration of the paralytic agent vecuronium bromide (0.1 mg/kg). General anesthesia was maintained with inhaled isoflurane (0.8%-1.5%) and intermittent boluses of fentanyl to maintain analgesia. The animals received continuous intravenous saline throughout the procedure and were monitored closely during experimental protocols. Animals were euthanized under anesthesia by cardioplegia with administration of a lethal dose of sodium pentobarbitol.

Stellate stimulation

Exposed LSG and RSG were electrically stimulated for 10 minutes using a platinum bipolar electrode connected to a Grass stimulator (S9D; Grass Technologies, West Warwick, RI). Stellate stimulation consisted of repeated square wave pulses (5-millisecond duration) delivered at 5 Hz with stimulus amplitude of 10 V similar to prior studies.[4,6] Animals were randomly assigned to receive LSG then RSG stimulation, or vice versa, with a 60-minute interval between stimulations.

Hemodynamic recordings

Systolic left ventricular (LV) pressures were assessed using a 5F pigtail, 12-pole conductance-pressure catheter connected to a MPVS Ultra processor (Millar Instruments, Inc, Houston, TX) placed in the left ventricle via carotid artery sheath under ultrasound guidance. Pressure was continuously monitored and recorded throughout experiments. Increases in LV pressures were noted at stimulation onset, confirming successful stimulation capture.

Electrocardiographic monitoring

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 V_1 through V_6 were placed posteriorly in the positions of V_6 through V_{11} to mirror standard anterior precordial lead electrode placement and record the horizontal plane.

Electrocardiograms were analyzed manually. QT interval was measured from onset of QRS to end of T in simultaneous leads and corrected for heart rate (QTc) using Bazett's formula: $QTc = QT/\sqrt{(RR)}$. ST-segment duration was measured from the end of the QRS to onset of the T-wave. Time from peak to end (Tp-Te) of T-wave was measured from maximal T-wave voltage to the end of T-wave.

T-wave vectorcardiography

T-wave vectors (mean electrical axis of repolarization) in both frontal and horizontal planes were measured as the angle perpendicular to the most isoelectric lead. If the most isoelectric T-wave was nearly but not completely isoelectric, further refinement of vector angle was calculated by comparing T-wave areas (duration and amplitude) of the most isoelectric lead and the closest adjacent lead.

Statistical analysis

Variables are reported as mean ± SEM. All groups of periodic data had a range less than 180°; thus, periodic variables were transformed rotationally into a common hemisphere not crossing 0° before mean and variance were calculated. Comparison of continuous variables before and after stellate stimulation was performed with Student t test for paired data. A 2-tailed $P < .05$ was considered statistically significant.

Results

Hemodynamic response to unilateral stellate stimulation

Left stellate ganglia and RSG were stimulated unilaterally for 10 minutes. In all animals, stimulation of the stellate ganglia caused a rapid increase in LV pressure (Fig. 1). Maximal pressure was reached 247 ± 58 seconds and 177 ± 29 seconds after LSG and RSG stimulation onset, respectively (P, not significant), before declining to steady-state values by the end of the stimulation period. Left ventricular peak pressure and at the end of 10 minutes of stimulation were significantly elevated and returned to baseline levels within 20 minutes of stimulation termination. Positive hemodynamic responses were used to confirm successful stimulation capture of the stellate ganglia.

Effect of unilateral sympathetic stimulation on T-wave morphometrics

Rapid changes in ventricular repolarization, indicated by changes in T-wave morphometrics, were noted within 15 seconds of stimulation onset during unilateral LSG or RSG stimulation (Fig. 2), returning to baseline after discontinuation of stimulation. The time course of these changes was very rapid in onset. Within several beats (<15 seconds), changes in T-wave amplitude, duration, and Tp-Te were