Subcutaneous nerve activity and spontaneous ventricular arrhythmias in ambulatory dogs

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BACKGROUND Stellate ganglion nerve activity (SGNA) is important in ventricular arrhythmogenesis. However, because thoracotomy is needed to access the stellate ganglion, it is difficult to use SGNA for risk stratification.

OBJECTIVE The purpose of this study was to test the hypothesis that subcutaneous nerve activity (SCNA) in canines can be used to estimate SGNA and predict ventricular arrhythmia.

METHODS We implanted radiotransmitters to continuously monitor left stellate ganglion and subcutaneous electrical activities in 7 ambulatory dogs with myocardial infarction, complete heart block, and nerve growth factor infusion to the left stellate ganglion.

RESULTS Spontaneous ventricular tachycardia (VT) or ventricular fibrillation (VF) was documented in each dog. SCNA preceded a combined 61 episodes of VT and VF, 61 frequent bigeminy or couplets, and 61 premature ventricular contractions within 15 seconds in 70%, 59%, and 61% of arrhythmias, respectively. Similar incidence of 75%, 69%, and 62% was noted for SGNA. Progressive increase in SCNA [48.9 (95% confidence interval [CI] 39.3–58.5) vs 61.8 (95% CI 45.9–77.6) vs 75.1 (95% CI 57.5–92.7) mV-s] and SGNA [48.6 (95% CI 40.9–56.3) vs 58.5 (95% CI 47.5–69.4) vs 69.0 (95% CI 53.8–84.2) mV-s] integrated over 20-second intervals was demonstrated 60 seconds, 40 seconds, and 20 seconds before VT/VF ($P < .05$), respectively. The Pearson correlation coefficient for integrated SCNA and SGNA was 0.73 ± 0.18 ($P < .0001$ for all dogs, n = 5). Both SCNA and SGNA exhibited circadian variation.

CONCLUSION SCNA can be used as an estimate of SGNA to predict susceptibility to VT and VF in a canine model of ventricular arrhythmia and sudden cardiac death.

KEYWORDS Atrioventricular block; Autonomic nervous system; Myocardial infarction; Sudden cardiac death; Ventricular arrhythmia

ABBREVIATIONS AIVR = accelerated idioventricular rhythm; **CI** = confidence interval; **ECG** = electrocardiogram; **FBG/C** = frequent bigeminy or couplets; **HASDA** = high-amplitude spike discharge activity; **iSCNA** = integrated subcutaneous nerve activity; **iSGNA** = integrated stellate ganglion nerve activity; **LABDA** = low-amplitude burst discharge activity; **PVC** = premature ventricular contraction; **SCD** = sudden cardiac death; **SCNA** = subcutaneous nerve activity; **SGNA** = stellate ganglion nerve activity; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

Sympathetic activation is associated with increased risk of ventricular arrhythmias and sudden cardiac death (SCD).[1] We have shown that stellate ganglion nerve activity (SGNA) precedes spontaneous ventricular tachycardia (VT) and ventricular fibrillation (VF) in an ambulatory canine model of SCD.[2] Because sympathetic nerve activity is important in arrhythmia initiation, it is highly desirable to develop a reliable and less invasive method to measure sympathetic outflow for arrhythmia prediction and risk stratification. Heart rate variability and microneurography have been used to assess sympathetic tone in patients. However, because of technical problems, those methods are not widely used for arrhythmia prediction.

The skin is well innervated by sympathetic nerve fibers.[3,4] Studies in dogs and rats demonstrated that the somata of the cutaneous sympathetic nerve fibers of the upper body are

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located in the middle cervical and stellate ganglia.[5,6] Innervation of the pectoralis muscle, which is located underneath the hypodermis in the upper chest wall, stems from the brachial plexus,[7] which communicates with the stellate ganglion.[5] In addition, light microscopy has revealed that large nerve trunks are present in the subcutaneous tissues.[5] These observations suggest that recording skin and/or muscle directed postganglionic sympathetic nerve activity, which we will collectively term as "subcutaneous nerve activity" (SCNA), from the hypodermis of the upper trunk may be used as a less invasive surrogate for SGNA to measure sympathetic outflow. We have recently shown that SCNA correlates well with SGNA and heart rate in normal ambulatory dogs.[8] However, it is not clear whether SCNA can be used to predict the onset of ventricular arrhythmias and SCD in diseased animals. The aim of the present study was to use an established canine model of SCD and investigate the relationship between SCNA, SGNA, ventricular arrhythmias, and SCD.

Methods

Surgical preparation

We reanalyzed data from 7 ambulatory dogs with complete heart block, myocardial infarction, and nerve growth factor infusion to the left stellate ganglion from a previous study.[2] The protocol was approved by the Institutional Animal Care and Use Committee of Cedars-Sinai Medical Center, Los Angeles, California. One pair of electrodes was used to record nerve activity from the left stellate ganglion; another pair of bipolar electrodes was implanted in the subcutaneous tissues of the right upper and left lower quadrant of the chest. In that study, the subcutaneous electrodes were placed for the purposes of electrocardiogram (ECG) recording.[2] In the current investigation, signals from those electrodes were high-pass filtered and inspected for nerve signals. The recording was made in a bipolar mode, with 2 widely spaced bipoles. The electrodes were the stainless steel wires that came with the Data Sciences International D70-EEE radiotransmitter (DSI, St. Paul, MN). The terminal 5 mm of the wires was stripped of its insulation and used for electrical recording. Subcutaneous interelectrode distance was not measured at the time of the study, but in similar size dogs it is estimated at 28 cm. A detailed description of study methods is available in the Online Supplementary Material.

Results

The simultaneous SGNA and SCNA recording lasted 43 ± 26 days

Presence and characteristics of subcutaneous nerve discharges

Similar to a previous report in normal canines, all 7 dogs demonstrated subcutaneous nerve discharges with similar morphology to the signals recorded from the left stellate ganglion.[8] In addition, SCNA morphology was similar to filtered skin and muscle sympathetic nerve activity obtained in microneurography studies.[9–11] We previously described 2 SGNA patterns in this canine model: low-amplitude burst discharge activity (LABDA) with amplitudes between 0.05 and 0.8 mV and high-amplitude spike discharge activity (HASDA) with amplitudes of 0.9 ± 0.16 mV.[2] Of 366 randomly selected 15-second frames, 214 contained SGNA and 186 displayed SCNA. In 88% of frames, the presence or absence of SGNA correlated directly with the presence or absence of SCNA. There were frames containing subcutaneous but not stellate ganglion discharges, suggesting that the origin of SCNA is not inadvertent recording of SGNA with the subcutaneous electrodes. All subcutaneous discharges demonstrated LABDA pattern with amplitude of 0.07 ± 0.08 mV. In all but 1 frame, which contained HASDA, SGNA also displayed LABDA pattern with amplitudes of 0.10 ± 0.11 mV. Unlike the SGNA channel, the SCNA channel was more prone to display incompletely filtered ECG signals and pacing artifacts. Figure 1 shows 2 VT episodes from 2 different animals. In the first animal (1A), the raw signal is high-pass filtered to obtain noncontaminated SCNA. In the second animal (1B), the ECG signals from the raw signals could not be filtered well and contaminate the SCNA channel with ECG artifacts (downward arrows) despite high-pass filtering. The onset of the SCNA discharge is still visible (upward arrow); however, integration of SCNA (in mV-s) cannot be accurately accomplished because of unfiltered ECG signals.

SCNA and SCD due to VF

Two dogs died of SCD due to VF on postoperative days 3 and 52. Figures 2 and 3 show the recordings immediately before and after the onset of VF in these 2 dogs. In both dogs, VF was preceded by both SGNA and SCNA. The tracings in 2A and 2B as well as 3A and 3B are continuous with the 2A and 3A panels preceding the 2B and 3B panels by 40 seconds. LABDA discharges before VF are marked by downward arrows (Figures 2 and 3). Massive SGNA and SCNA (asterisks) occurred after VF, likely responses to acute reduction of blood pressure. Similar to Figure 1B, the dog portrayed in Figure 2 was not included in the quantitative nerve integration analyses because the SCNA channel was contaminated with ECG and pacing artifacts.

SCNA and VT

Two episodes of VF and 59 episodes of VT from 6 dogs (7–12 per dog), occurring 23 ± 17 days after surgery with an average heart rate of 156 ± 44 bpm and duration of 20 ± 89 seconds, were analyzed. A total of 75% of VT/VF episodes were preceded by SGNA and 70% by SCNA within 15 seconds of initiation. Of 61 15-second episodes of AIVR selected within 26 ± 26 minutes, 59% contained SGNA and 43% had SCNA. By using a generalized linear mixed-effects model, the odds ratio of observing SGNA and SCNA 15 seconds before VT/VF compared to observing discharges during episodes of AIVR for a specific dog was 2.32 (95% confidence interval [CI] 1.01–5.31, $P = .0466$) and 3.13 (95% CI 1.45–6.76, $P = .004$), respectively. Figure 4A shows another representative episode of VT, along with a