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Effects of Stellate Ganglion Cryoablation on Subcutaneous Nerve Activity and Atrial Tachyarrhythmias in a Canine Model of Pacing-Induced Heart Failure

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ABSTRACT

OBJECTIVES This study aimed to test the hypothesis that subcutaneous nerve activity (SCNA) can adequately estimate the cardiac sympathetic tone and the effects of cryoablation of the stellate ganglion in dogs with pacing-induced heart failure (HF).

BACKGROUND Recording of SCNA is a new method to estimate sympathetic tone in dogs. HF is known to increase sympathetic tone and atrial arrhythmias.

METHODS Twelve dogs with pacing-induced HF were studied using implanted radiotransmitters to record the stellate ganglia nerve activity (SGNA), vagal nerve activity, and SCNA. Of these, 6 dogs (ablation group) underwent bilateral stellate ganglia cryoablation before the rapid ventricular pacing; the remaining 6 dogs (control group) had rapid ventricular pacing only. In both groups, SCNA was compared with SGNA and the occurrence of arrhythmias.

RESULTS SCNA invariably increased before the 360 identified atrial tachyarrhythmia episodes in the 6 control dogs before and after HF induction. SCNA and SGNA correlated in all dogs with an average correlation coefficient of 0.64 (95% confidence interval: 0.58 to 0.70). Cryoablation of bilateral stellate ganglia significantly reduced SCNA from 0.34 ± 0.033 μV to 0.25 ± 0.028 μV ($p = 0.03$) and eliminated all atrial tachyarrhythmias.

CONCLUSIONS SCNA can be used to estimate cardiac sympathetic tone in dogs with pacing-induced HF. Cryoablation of the stellate ganglia reduced SCNA and arrhythmia vulnerability. (J Am Coll Cardiol EP 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

Sympathetic tone measured by stellate ganglion nerve activity (SGNA) has been shown to influence atrial electrophysiology and the onset of atrial arrhythmias. We (1-3) recently proposed a new method to simultaneously record electrocardiogram (ECG) and subcutaneous nerve activity (SCNA) using bipolar electrodes placed under the skin. The electrical signals were low-pass filtered to optimize ECG and high-pass filtered to reveal SCNA. Because a good correlation has been shown between SCNA and the simultaneously recorded SGNA (1), we proposed that SCNA may be used to estimate cardiac sympathetic tone.

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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ABBREVIATIONS AND ACRONYMS

aSGNA = averaged stellate ganglia nerve activity

aSCNA = averaged subcutaneous nerve activity

aVNA = averaged vagus nerve activity

ECG = electrocardiogram

HF = heart failure

LCSD = left cardiac sympathetic denervation

LSG = left stellate ganglion

PAT = paroxysmal atrial tachycardia

RSG = right stellate ganglion

SCNA = subcutaneous nerve activity

SGNA = stellate ganglia nerve activity

VNA = vagus nerve activity

The noninvasive estimation of sympathetic tone may provide new insights into the mechanisms of cardiac arrhythmias and may also provide a direct method to measure the success of neuromodulation procedures. Ogawa et al. (4,5) previously performed 2 studies in dogs with pacing-induced heart failure (HF). In the first study, it was shown that HF increases SGNA and occurrence of cardiac arrhythmias (4). In a second study using the same HF model, cryoablation of the caudal half of the left and right stellate ganglia and T2 to T4 thoracic sympathetic ganglia was performed. It was shown that cryoablation significantly reduced both SGNA and paroxysmal atrial tachycardia (PAT) episodes (5). The data from these studies have not been analyzed to determine if SCNA increased after induction of HF and decreased after cryoablation of the stellate ganglion. We retrieved the data from both studies and manually analyzed de novo the SGNA and atrial tachyarrhythmia episodes. We also performed analyses of SCNA using methods previously reported (1). The purpose of the present study was to test the hypothesis that: 1) HF increases both SCNA and SGNA; 2) both SCNA and SGNA preceded the onset of PAT at baseline and after induction of HF; and 3) cryoablation of the stellate ganglion can reduce both SCNA and SGNA in ambulatory dogs.

METHODS

Original data from 2 previously published reports (4,5) were retrieved and manually analyzed. The research protocols were approved by the Institutional Animal Use and Care Committees of the Cedars-Sinai Medical Center, Los Angeles, California, and the Indiana University School of Medicine at the Methodist Research Institute, Indianapolis, Indiana.

SURGICAL PREPARATIONS. The surgical preparations have been described previously. Briefly, all surgeries were performed under isoflurane anesthesia. Subcutaneous bipolar electrodes were placed in the left thorax of dogs, 6 to 10 cm apart, to record SCNA. The electrodes were stainless steel wires with the terminal 5 mm of the wires stripped of their insulation and used for electrical recording. The leads were attached to a Data Science International D70-EEE radiotransmitter (DSI, St. Paul, Minnesota), which was also implanted in the subcutaneous space. In the same procedure, through a left thoracotomy, a pair of bipolar electrodes from the DSI radiotransmitter was sutured onto the left stellate ganglion (LSG) to record SGNA. Another set of bipolar electrodes was placed on the left thoracic vagal nerve to record vagal nerve activity (VNA).

EXPERIMENTAL PROTOCOLS. In all dogs, a pacing lead was implanted in the right ventricular apex and connected to a Medtronic Itrel neurostimulator for high-rate ventricular pacing. After recovery from the initial surgery, the dogs had 2 weeks of continuous baseline ambulatory monitoring. After the baseline recording, the first group of 6 dogs (group 1) underwent right ventricular pacing at 150 beats/min for 3 days, at 200 beats/min for 3 days, and then at 250 beats/min for 3 weeks to induce HF, which was confirmed by ECG (6). The pacemakers were then turned off to allow ambulatory monitoring for an additional 2 weeks. In the second group of 6 dogs (group 2), the caudal half of the left stellate ganglion and T2 to T4 thoracic sympathetic ganglia were cryoablated through the left thoracotomy using a 7-cm SurgiFrost probe (CryoCath Technologies, Inc., Montreal, Canada) during the same surgery in which the DSI radiotransmitter was implanted for monitoring of SCNA, SGNA, and VNA. The dogs then underwent the same surgery and protocol for implantation of the Medtronic Itrel neurostimulator for subsequent high-rate ventricular pacing to induce HF. These dogs were also monitored for 2 weeks before and after HF induction.

DATA ANALYSES. Recordings from the bipolar electrodes connected to the radiotransmitter were analyzed to obtain SCNA, SGNA, VNA, and ECG using custom-written software. The impedance of the electrodes was 0.7 to 0.8 Ω and the recordings were amplified 10,000 times and sampled at 1,000 Hz. We obtained an ECG for analyses by applying a bandpass filter (5 to 100 Hz) on the vagus nerve channel or subcutaneous nerve channel of the radiotransmitter. SCNA, SGNA, and VNA were obtained by high-pass filtering at 150 Hz. The SGNA and VNA were rectified and integrated over 1 min. The SCNA was also rectified and integrated over the same minute after adjusting the SCNA with wavelet analysis as described previously (7). In particular, spike-triggered averaging was performed to allow removal of the ventricular electrogram from the SCNA by subtracting a ventricular electrogram template obtained from averaged ventricular electrograms in the observational window. Finally, the ECG was used to calculate the heart rate over the same minute. The sum of all digitized nerve activity was then divided by the total number of samples during the same period to obtain averaged SGNA (aSGNA), averaged SCNA (aSCNA), and averaged VNA (aVNA) per sample.