Spinal cord stimulation protects against ventricular arrhythmias by suppressing left stellate ganglion neural activity in an acute myocardial infarction canine model

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BACKGROUND Previous studies have shown that spinal cord stimulation (SCS) may reduce ventricular arrhythmias (VAs) induced by acute myocardial infarction (AMI). Furthermore, activation of left stellate ganglion (LSG) appears to facilitate VAs after AMI.

OBJECTIVE The purpose of this study was to investigate whether pretreatment with SCS could protect against VAs by reducing LSG neural activity in an AMI canine model.

METHODS Thirty dogs were anesthetized and randomly divided into SCS group (with SCS, n = 15) and sham group (sham operation without SCS, n = 15). SCS was performed for 1 hour before AMI. Heart rate variability (HRV), ventricular effective refractory period (ERP), serum norepinephrine level, LSG function measured by blood pressure increases in response to LSG stimulation, and LSG neural activity were measured for 1 minute at baseline and 1 hour after SCS. AMI was induced by left anterior descending coronary artery ligation, and then HRV, LSG neural activity, and VAs were measured.

RESULTS Compared to baseline, SCS for 1 hour significantly prolonged ventricular ERP, increased HRV, and attenuated LSG function and LSG activity in the SCS group, whereas no significant change was shown in the sham group. AMI resulted in a significant decrease in HRV and increase in LSG neural activity in the sham group, which were attenuated in the SCS group (frequency: 99 ± 34 impulses/min vs 62 ± 22 impulses/min; amplitude: 0.41 ± 0.12 mV vs 0.18 ± 0.05 mV; both $P < .05$). The incidence of VAs was significantly lower in the SCS group than in the sham group.

CONCLUSION SCS may prevent AMI-induced VAs, possibly by suppressing LSG activity.

KEYWORDS Spinal cord stimulation; Ventricular arrhythmia; Left stellate ganglion

ABBREVIATIONS **AMI** = acute myocardial infarction; **BP** = blood pressure; **ERP** = effective refractory period; **HF** = high-frequency component; **HRV** = heart rate variability; **LF** = low-frequency component; **LF/HF** = ratio between LF and HF powers; **LSG** = left stellate ganglion; **LVA** = left ventricular apex; **LVB** = left ventricular base; **LVM** = median area of left ventricle; **MAP** = monophasic action potential; **MAPD** = monophasic action potential duration; **NE** = norepinephrine; **RVA** = right ventricular apex; **RVB** = right ventricular base; **RVM** = median area of right ventricle; **SCS** = spinal cord stimulation; **VA** = ventricular arrhythmia; **VF** = ventricular fibrillation; **VPB** = ventricular premature beat; **VT** = ventricular tachycardia

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Introduction

Spinal cord stimulation (SCS) has been used globally for decades to cure peripheral vascular disease, refractory angina, Raynaud disease, and neuropathic pain.[1] Recently, SCS has also been investigated for the treatment of ventricular arrhythmias (VAs).[2,3] Initial studies showed that SCS can reduce the combined incidence of ischemia-induced ventricular tachycardia (VT) and ventricular fibrillation (VF) from 59% to 23%[2] and is more effective than beta-blockers in preventing spontaneous VTs in dogs with prior myocardial infarction.[3] Clinically, 1 report demonstrated that 2-month treatment with chronic SCS was associated with a reduction of VT and VF events in 2 patients experiencing high VT and VF burden.[4] Ferrero et al[5] also demonstrated that 2 hours of SCS could significantly suppress the amplitude of T-wave alternans in patients and suggested that SCS could stabilize electrophysiologic properties and

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thereby reduce the incidence of VT/VF in humans. However, the precise mechanism underlying the antiarrhythmic effects of SCS remains unknown. Numerous studies have established that activation of the cardiac sympathetic nervous system, especially the left stellate ganglion (LSG), appears to facilitate the genesis of VAs and sudden cardiac death.[6,7] Conversely, inhibition of the sympathetic nervous system appears to be protective.[7] Furthermore, previous studies reported that whole-body norepinephrine (NE) spillover could be mitigated by SCS, and SCS might exert an antisympathetic effect.[8,9] Thus, in the present study, we sought to investigate whether preconditioning with SCS could prevent VAs by reducing LSG activity in an acute myocardial infarction (AMI) canine model.

Methods

Animal preparation

Thirty canines weighing between 20 and 25 kg were included in the study. The experiments performed in the present study were approved by the Animal Ethics Committee of Wuhan University under approval number 2014-0276 and followed the guidelines outlined by the Care and Use of Laboratory Animals of the National Institutes of Health. All surgeries were performed with animals under anesthesia with 3% sodium pentobarbital at an initial dose of 1 mL/kg and a maintenance dose of 2 mL/h. A body surface ECG was recorded throughout the procedure using a computer-based Lab System (Lead 2000B, Jingjiang Inc, Wuhan, China), and core body temperature of the dogs was maintained at 36.5°C ± 1.5°C. Bilateral thoracotomy was conducted at the fourth intercostal space.

SCS

A quadripolar electrode was introduced through the needle under fluoroscopic guidance to achieve a spinal epidural at the T1–T5 spinal cord level. The rostral electrode of the lead was positioned at the T1 level with the caudal electrode at the T5 level. The tip of the lead was positioned slightly to the left of midline, similar to the clinical routine used in humans,[10] using anteroposterior fluoroscopy. The location of the electrode tip was verified via an electrical current delivered to the rostral and caudal poles using a stimulus isolation unit and constant current generator connected to a stimulator (S88, Grass Instruments, Quincy, MA). The rostral and caudal electrodes were chosen as cathode and anode, respectively (Figure 1A). SCS was delivered at 50 Hz, 0.2-ms pulse width with the amplitude approximately 90% of motor threshold, the lowest current that induced muscle contractions in the proximal forepaw and shoulder. In the sham group, the electrode was positioned to the epidural space to the T1–T5 spinal cord level without stimulation.

Measurements of heart rate variability

Heart rate variability (HRV) was examined and analyzed to assess cardiac autonomic activity. Spectral power for HRV was analyzed on 5-minute ECG recording segments obtained

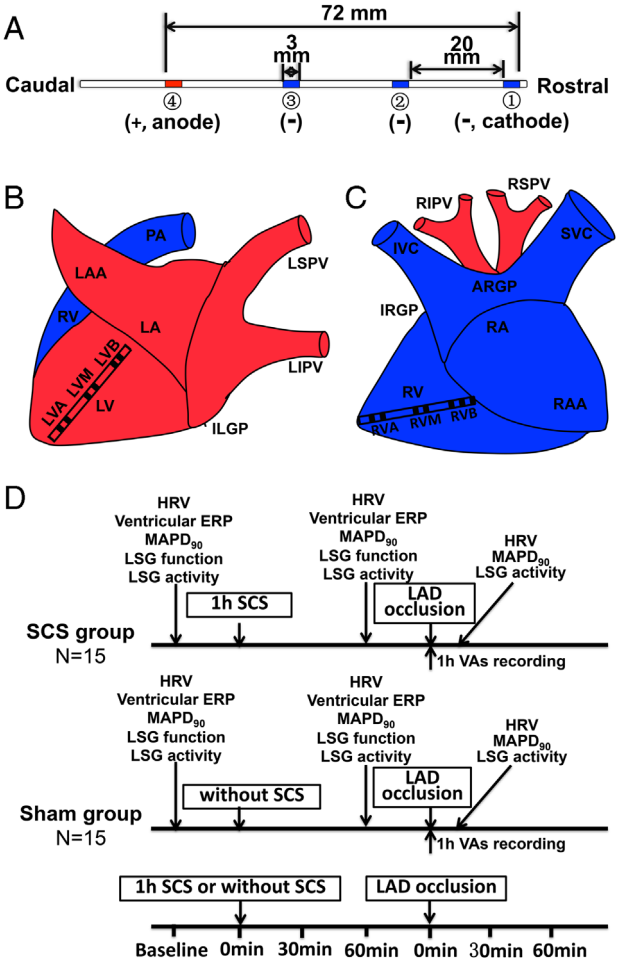

Figure 1 Schematic representation of the quadripolar electrode for spinal cord stimulation (SCS) **(A),** location of the electrodes on the ventricle **(B, C),** and experimental design flowchart **(D).** ERP = effective refractory period; HRV = heart rate variability; IVC = inferior vena cava; LA = left atrium; LAA = left atrial appendage; LAD = left anterior descending artery; LIPV = left inferior pulmonary vein; LSG = left stellate ganglion; LSPV = left superior pulmonary vein; LV = left ventricle; LVA = left ventricular apex; LVB = left ventricular base; LVM = median area between LVA and LVB; PA = pulmonary artery; RA = right atrium; RAA = right atrial appendage; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; RV = right ventricle; RVA = right ventricular apex; RVB = right ventricular base; RVM = median area between RVA and RVB; SCS group = with spinal cord stimulation; sham group = sham operation without spinal cord stimulation; SVC = superior vena cava; VA = ventricular arrhythmia.

at baseline and 1 hour after SCS, and an autoregressive algorithm was used to analyze digitized signals from the ECG recordings. The following power spectral variables were determined: high-frequency component (HF), low-frequency component (LF), and ratio between LF and HF (LF/HF, index of interaction between sympathetic and vagal activity).[11]

Measurement of ventricular effective refractory period

Multielectrode catheters were sutured at the left and right ventricular free walls. The ventricular effective refractory period (ERP) was recorded from the following 6 sites