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Prevention of ventricular arrhythmia complicating acute myocardial infarction by local cardiac denervation

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ABSTRACT

Background: Augmentation of sympathetic nerve activity after acute myocardial infarction (AMI) contributes to fatal arrhythmia. In this study, we investigated whether local ablation of the coronary sinus (CS) and great cardiac vein (GCV) peripheral nerves could reduce ventricular arrhythmias (VA) in a canine AMI model.
Methods: Twenty-one anesthetized dogs were randomly assigned into the sham-operated, MI and MI-ablation groups, respectively. The incidence and duration of VA were monitored among different groups. The ventricular effective refractory period (ERP), the ERP dispersion and the ventricular fibrillation threshold (VFT) were measured during the experiments. Norepinephrine (NE) levels in CS blood and cardiac tissue were also detected in this study.
Results: The incidence and duration of VA in MI-ablation group were significantly reduced as compared to the MI dogs ($p < 0.05$). Furthermore, local cardiac denervation drastically prolonged the ventricular ERP in the ischemia area, decreased the ERP dispersion, and reduced NE levels in CS blood ($P < 0.05$). VFT also showed an increased trend in the AMI-ablation group.
Conclusions: The results of this study indicate that, in the canine AMI model, local ablation of CS and GCV peripheral nerves reduces VA occurrence and improves ventricular electrical stability with no obvious effects on heart rate, mean arterial pressure and infarct size. This study suggests that local cardiac denervation may prevent ventricular arrhythmias complicating AMI.

1. Introduction

Ventricular arrhythmia (VA) is a common complication of acute myocardial infarction (AMI), and primary VA is a major cause of sudden cardiac death (SCD) in AMI patients [1–5]. Prevention and management of primary VA after AMI is a key regimen to decrease SCD incidence. However, in terms of the overall survival rate, antiarrhythmic drugs fail to prevent VA-induced SCD in patients without an ICD (implantable cardioverter defibrillator) [6–8]. Novel methodologies are needed to prevent the occurrence of VA complicating AMI.

Beta-blockers significantly improve outcome of AMI patients partially due to inhibiting sympathetic nerve activity [9–12]. This suggests that the sympathetic nervous system might play an important role in the genesis and maintenance of VA in AMI patients. Direct inhibition of sympathetic nerve activity, for instance, by renal denervation or high thoracic epidural anesthesia, drastically decreases VA incidence after AMI in animal models and in clinical patients [13–16]. These studies indicate that, in beta-blocker intolerant or contraindicated patients, denervation is an alternative approach to prevent VA occurrence. Although inhibition of autonomous nerve fibers at sites far from the heart clearly shows anti-arrhythmia effects, the potential damage to other organs limits its application in clinical practice.

To overcome the limitations of previous methodologies, in this study, we tested whether local ablation of cardiac sympathetic nerves reduces VA incidence after AMI. In humans and animals, major sympathetic nerve fibers course toward the heart alongside the great vessels, and cross over the coronary sinus (CS) [17–19]. Using the canine AMI model, we directly ablated the CS and GCV peripheral nerves with radiofrequency ablation. Local cardiac denervation was found to significantly reduce VA occurrence and improved ventricular electrical stability without obvious effects on heart rate, mean arterial pressure and ischemia area.

2. Materials and methods

2.1. Experimental animals

Mongrel dogs of both sexes were obtained from the experimental animal center at the First Affiliated Hospital, Harbin Medical University, China. All experimental protocols were approved by the Animal

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Experimentation Ethics Committee under the declaration of Helsinki and the guiding principles in the care and use of animals.

Twenty-one dogs, weighing between 15 and 25 kg, were anesthetized with sodium pentobarbital (25 mg/kg induction; 1.0 mg/kg/h with intermittent boluses, as needed), and then intubated and mechanically ventilated (Electrical Animal Ventilator, Medical Equipment Factory, Shanghai, China) to maintain the arterial pCO_2 between 35 and 40 mm Hg. Fluid resuscitation was established with 0.9 N NaCl at 10 ml/kg/h. The systemic arterial pressure was monitored during the experiment with a computer-based Lab System (GY-6328, Huanan Inc., China). The core body temperature of the animals was maintained at 36.5 ± 1.5 °C with heating pads.

2.2. Generation of myocardial infarction and local ablation of cardiac sympathetic nerves

Twenty one animals were randomly assigned into the groups of sham-operated (n = 5), myocardial infarction (MI, n = 8) and myocardial infarction followed by nerve ablation (MI-ablation, n = 8). To establish AMI in both MI and MI-ablation group, the left anterior descending coronary artery (LAD) was permanently ligated just below the first diagonal branch by the one-stage procedure in open-chest and anesthetized dogs [20]. The animals in sham-operated group also underwent thoracotomy and pericardiotomy, but not coronary artery ligation.

After successfully creating AMI, we gave the animals a 90-minute interval to recover. The dogs in the MI-ablation group then further underwent cardiac nerve ablation. The ablation sites were determined by the anatomical distribution of autonomic nerves along the CS (the distal CS, proximal 2 cm from the coronary sinus ostium) and the GCV (upper third anterior interventricular groove). To avoid potential damage to the proximal left anterior descending (LAD) and left circumflex (LCX) arteries, which distribute in the target area, the ablation sites were also chosen 0.5 cm away from these arteries. The radiofrequency (RF) energy of a cardiac ablation generator (IBI—1500T8,Irvine Biomedical Inc., USA) was set to 20 W with a cut-off temperature at 60 °C, and a saline irrigation catheter (7-F, 4.0-mm tip electrode, Irvine Biomedical Inc. USA) was applied to ablate the nerves for 2 min at both sides of the CS and GCV, respectively. An open irrigation system was set to continuously irrigate the ablation catheter at 40–60 mL/min during radiofrequency delivery.

2.3. Electrophysiological study

Electrocardiogram (ECG) was recorded in all dogs during experiment to determine the incidence and duration of VA, including ventricular premature contraction (VPC), paroxysmal ventricular tachycardia (PVT) and spontaneous VF.

Before creating the MI and 2 h after cardiac denervation, multi-electrode catheters with a 2 mm interelectrode distance were sutured to record the effective refractory period (ERP) of the ventricular myocardium at 6 epicardial sites. These sites were equally split into three groups which distributed respectively in the ischemia area (IA, below the first diagonal branch artery), the ischemia border area (IBA, the peripheries of the ischemia area) and the ischemia remote area (IRA, around the upper apex) (Fig. 1A). For comparison, in the sham-operated dogs which did not undergo cardiac infarction, electrodes were put on the same epicardial sites as in the MI and MI-ablation dogs. Programmed electrical stimulation was performed to measure the ERP and to induce VF threshold (VFT) in all animals. Briefly, we used an 8-beat drive train (S1, 300-ms cycle length) followed by an extra stimulus (S2), and then repeated this procedure with progressively shorter S1–S2 intervals (from 250 ms to ventricular ERP). Ventricular ERP was defined as the longest S1–S2 interval that failed to capture the ventricles. The ERP dispersion was computed as coefficient of variation (CV, standard deviation/mean) of the ERPs at all six recording sites, and the ERP dispersion was also expressed as CV-ERP [21,22].

The VFT, the minimum voltage to induce sustained VF, was determined in the dogs without spontaneous VF [21]. VF was induced at the same heart rate (200 beats/min) among animals. Followed by a 20-beat drive train with a pacing cycle length of 300 ms, 100 ms S1–S1 stimuli were repeatedly applied to the right ventricular apex with an increase of stimuli intensity by 2 V each time until VF was induced. Each stimulus lasted for 10 second and was followed by a 30-second rest period before the next round of stimulation. Once a sustained VF was induced, a cardiac electric defibrillator was used to shock the heart back to normal rhythm. After a 5-minute break, the stimulation protocol was repeated to measure the second VFT. The measurements of both times were averaged as mean VFT. At the end of the experiment, all dogs died of sustained VF.

2.4. Measurement of plasma and tissue homogenates Norepinephrine (NE)

Two hours after the ablation, blood samples were drawn into heparinized tubes through a modified Morawitz cannula, which was introduced into the CS through the azygos vein. All samples were placed immediately on ice after collection and centrifuged at 4 °C within 30 min. Plasma was collected and stored at −20 °C for further analysis.

At the end of the experiment, ventricle tissues at the 6 epicardial electrode sites were harvested and analyzed separately. 100 mg tissue was rinsed with PBS to remove excess blood, homogenized in PBS and stored overnight at −20 °C. After two freeze–thaw cycles to break the cell membrane, the homogenates were centrifuged for 5 min at 5000 *g* at 4 °C, and the supernatant was collected and stored at −20 °C.

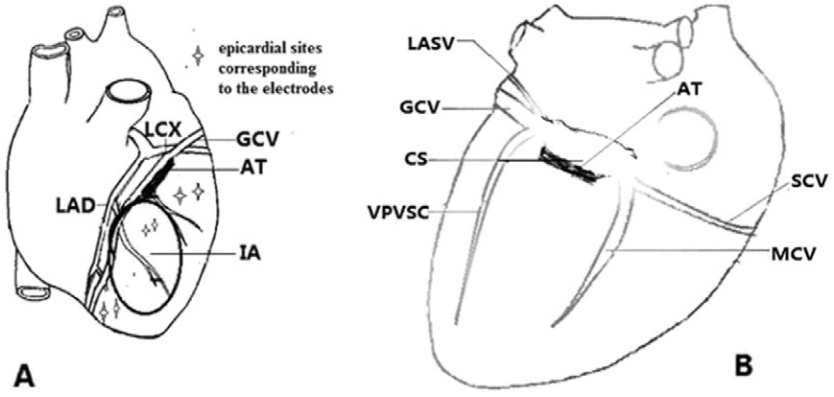

Fig. 1. A sketch of the anterior (A) and posterior (B) of a dog heart to show ablation targets, multi-electrodes, ischemia area, coronary artery and coronary sinus and its tributaries. AT, ablation target; IA, ischemia area; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; CS, coronary sinus; GCV, great cardiac vein; MCV, middle cardiac vein; SCV, small cardiac vein; LASV, left atrium slanting veins; VPVSC, vena posterior ventriculi sinistri cordis.