Autonomic Neuroscience: Basic and Clinical 205 (2017) 26–32

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Cardiac autonomic ganglia ablation suppresses atrial fibrillation in a canine model of acute intermittent hypoxia

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ARTICLE INFO

Article history:
Received 7 December 2016
Received in revised form 26 January 2017
Accepted 21 February 2017

Keywords:
Atrial fibrillation
Hypoxia
Autonomic nervous system
Ganglionated plexus

ABSTRACT

Background: Atrial fibrillation (AF) is associated with hypoxia in which cardiac autonomic nerve system (ANS) plays an important role. Our previous studies indicated that ANS is activated in an intermittent hypoxia model and contributes to AF initiation. This study aimed to investigate the effects of cardiac ganglionated plexus (GP) ablation on AF in this model.

Methods and results: In thirteen anesthetized male dogs, GP ablation was applied after 1 h of intermittent hypoxia in the first group ($n = 7$) and before that in the second group ($n = 6$). The heart rate (HR), blood pressure (BP), arterial blood gases, heart rate viability indices, atrial effective refractory period (ERP) and window of vulnerability (WOV), the sum of WOVs (ΣWOV) were measured. In both groups, HR, BP increased and then declined during hypoxia, and not significantly affected by GP ablation. Hypoxemia, hypercapnia and acidosis were observed after intermittent hypoxia. In the first group, both of low frequency power (LF) and high frequency power (HF) increased during hypoxia. At the end of intermittent hypoxia, LF/HF ratio decreased, ERP shortened and ΣWOV increased. The following GP ablation resulted in increases in LF, LF/HF, ERP and decreases in HF, ΣWOV. In the second group, GP ablation caused increases in LF, LF/HF, ERP and decrease in HF. Subsequently, ERP shortened at several sites after intermittent hypoxia. However, there were no significant changes in LF/HF ratio or ΣWOV.

Conclusions: Cardiac ANS plays an important role in hypoxia-induced AF. AF associated with hypoxia might be prevented or reversed by GP ablation.

1. Introduction

Atrial fibrillation (AF) is frequently encountered in clinical practice. Numerous studies have found that obstructive sleep apnea (OSA) is a strong predictor of failure in AF treatment, including catheter ablation (Fein et al., 2013; Naruse et al., 2013; Szymanski et al., 2015), cardioversion (Kanagala et al., 2003) and anti-arrhythmic drugs (Monahan et al., 2012a). OSA is the major form of sleep-related breathing disorders and characterized by repetitive collapses of the upper airway that result in negative thoracic pressure and intermittent hypoxia (Linz et al., 2013).

Some studies have indicated that autonomic nervous system (ANS) is involved in AF associated with hypoxia (Gao et al., 2015; Linz et al., 2012; Lu et al., 2013). In our previous study (Lu et al., 2013), we established an acute intermittent hypoxia animal model with similar pathophysiological characteristics to OSA patients, such as hypoxemia, hypercapnia and acidosis. Using this model, we found that over activation of vagal tone and consequent autonomic imbalance were important influence factors of AF associated with hypoxia.

Atrial ganglionated plexus (GP) not only constitute the main part of intrinsic cardiac ANS but also modulate the autonomic interactions between the extrinsic and intrinsic cardiac ANS (Hou et al., 2007; Shen and Zipes, 2014), and play important roles in the initiation and maintenance of AF (Po et al., 2006; Scherlag et al., 2008). GP ablation was shown to be effective to inhibit rapid firing-mediated AF (Lu et al., 2009). Ablation of the GP at the right pulmonary artery could inhibited AF in a model of acute apnea lasting for 2 min (Ghias et al., 2009). However, effects of atrial GP ablation on intermittent hypoxia-induced AF have not been revealed yet. In this study, ablation of four atrial GP was performed in this acute intermittent hypoxia model, changes of ANS and its effects on atrial electrophysiological properties and AF vulnerability were investigated.

2. Materials and methods

2.1. Animal preparation

The protocol of this study was approved by the Committee on the Ethics of Animal Experiments of the Wuhan University. And animal

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http://dx.doi.org/10.1016/j.autneu.2017.02.006
1566-0702/

studies were performed in accordance with recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. Thirteen adult male mongrel dogs weighing 20–25 kg were bred and supplied by the center of experimental animal in medical college of Wuhan University. All dogs were intravenously anesthetized with sodium pentobarbital (30 mg/kg) and ventilated with an adjustable ventilator (MAO01746, Harvard Apparatus, Holliston, USA). Additional doses of 2 mg/kg of Na-pentobarbital were administered at the end of each hour. The left femoral vein was cannulated for a saline drip to maintain the fluid balance, and the right femoral artery was used for blood pressure recording and arterial blood sampling. Electrocardiogram (ECG) limb leads were persistently recorded.

The chest was cut open through left and right thoracotomies at the fourth intercostal space to expose the heart. Nine multi-electrode catheters were sutured at the surfaces of the left and right atrial appendages (LAA and RAA, respectively), the left and right atria (LA and RA, respectively), the left and right superior pulmonary veins (LSPV and RSPV, respectively), the left and right inferior pulmonary veins (LIPV and RIPV, respectively), and the superior vena cava (SVC) for electrical pacing and recording (Fig. 1). All tracings from the electrode catheters were amplified and digitally recorded using a multi-channel electrophysiology recorder (Lead 7000, Jingjiang Inc., Sichuan province, China) filtered at 70 to 600 Hz.

2.2. Ventilator settings

Different states were simulated by adjusting the ventilator parameters. The normal settings were as follows: tidal volume 10 ml/kg, rate 16 bpm, and inspiratory/expiratory rate 1:1.5. The intermittent hypoxia settings were as follows: tidal volume 5 ml/kg, rate 16 bpm, inspiratory/expiratory rate: 1:1.5, and temporary suspension for 10 s at the end of each expiration every 30 s, similar to our previous study (Lu et al., 2013).

2.3. Location and ablation of GP

There are typically four major atrial GPs that are located inside the epicardial fat pads near the pulmonary veins (Cui et al., 2011) (Fig. 1). High-frequency electrical stimulation (20 Hz, 0.1 ms duration, 1–12 V) was applied to identify GPs. Positive reactions were defined by the slowing of heart rate proportional to the stimulating voltages. After GP identification, radiofrequency energy was delivered to ablate the targeted GP. Effective ablation was confirmed by disappearance of all positive reactions under the strongest stimulation. Stimulus and ablation of all the four atrial GP were conducted using the same method as above. The damaged area was limited by visually destroy of target fat pad without damage of collateral tissue, which was confirmed by the fact that the morphology and amplitude of the electrograms at the atrial sites closest to the fat pad were not altered after ablation.

2.4. Heart rate variability (HRV) analysis

Five minutes of ECG records were collected for HRV spectrum analysis to reveal the activity of ANS. High frequency power (HF, 0.15 to 0.4 Hz), low frequency power (0.04 to 0.15 Hz) and low frequency/high frequency ratio (LF/HF) were calculated.

2.5. Blood gas analysis

Arterial blood was drawn from the femoral artery sheath with an anaerobic heparinized syringe. The pH value, partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), and oxyhemoglobin saturation (SaO_2) were analyzed within 5 min after collection.

2.6. Cardiac electrical recording

ERPs of each site were determined by programmed pacing from the multi-channel electrophysiology recorder (Lead 7000, Jingjiang Inc., Sichuan Province, China). There were eight sequential stimuli (S1-S1, cycle length 330 ms) followed by one premature stimulus (S2) with doubling pacing threshold. The S1-S2 interval progressively decreased by 10 ms then by 2 ms when near the refractory value to ensure accurate recording. ERPs were the longest S1-S2 interval that failed to capture the atria. Window of vulnerability (WOV), defined as the difference between the longest and shortest S1-S2 intervals when AF was induced, was used as a quantitative measure of AF inducibility. WOV was measured if AF was induced by decremental S1S2 stimulation. Atrial fibrillation was defined as >5 s of irregular atrial rate faster than 500 per minute (>500 bpm) with irregular atrioventricular conduction. ERP and WOV of all nine sites (i.e., LSPV, LIPV, LA, LAA, RSPV, RIPV, RA, RAA and SVC) were determined. ΣWOV, sum of WOVs at all sites was used to evaluate the overall AF inducibility. ERP and WOV measurements were completed within 15 min.

2.7. Experiment protocol

Thirteen dogs were randomly assigned to two groups. The first group included seven dogs in which GP ablation was performed after 1 h of intermittent hypoxia. Arterial blood samples were taken from the femoral arteries, 5 min of ECG data were collected, ERP and WOV data from all sites were determined in the baseline state, after hypoxia and after GP ablation, respectively. The second group included six dogs that underwent GP ablation before 1 h of intermittent hypoxia. Arterial blood samples, ECG data, ERP and WOV from the nine sites were collected at baseline, after GP ablation, and at the end of hypoxia,

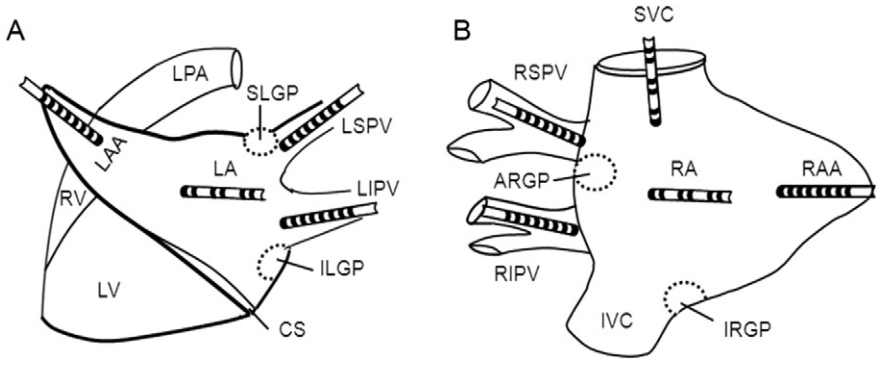

Fig. 1. Schematic representation and catheters position. A: Left thoracotomy approach. B: Right thoracotomy approach. LA = left atrium; LAA = left appendage; LV = left ventricle; RV = right ventricle; LPA = left pulmonary artery; CS = coronary sinus; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; SLGP = superior left GP; ILGP = inferior left GP; RA = right atrium; RAA = right appendage; SVC = superior vena cava; IVC = inferior vena cava; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; ARGP = anterior right GP; IRGP = inferior right GP.