Paradoxical long-term proarrhythmic effects after ablating the "head station" ganglionated plexi of the vagal innervation to the heart

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BACKGROUND The ganglionated plexi (GP) located at the junction of the superior vena cava, aorta, and right pulmonary artery (SVC-Ao GP) was proposed to be the "head station" between the extrinsic and the intrinsic cardiac autonomic nervous system (ECANS and ICANS, respectively).

OBJECTIVE To investigate the chronic effects after interrupting the ECANS-ICANS connections by ablating the SVC-Ao GP.

METHODS A right thoracotomy in 10 dogs allowed stimulation at the right superior and inferior pulmonary veins (RSPV and RIPV, respectively), right atrial appendage (RAA), and SVC to determine effective refractory period (ERP) and atrial fibrillation (AF) inducibility in the first operation. Group 1 (n = 5) received SVC-Ao GP ablation; group 2 (n = 5) received no ablation. A second operation and the same measurements were made 10 weeks later. A pacemaker with lead implanted at the RSPV recorded atrial fibrillation or tachycardia (AF/AT).

RESULTS During the first operation in group 1, ERPs increased significantly in the SVC but not at the RSPV, RIPV, or RAA site immediately after ablation, whereas ERPs decreased significantly in the RSPV, RIPV, and RAA but not the SVC in the second operation performed 10 weeks later (compared to the ERP in the first operation). ERPs decreased and AF/AT burden increased significantly from weeks 4 and 5, respectively, after the first operation in group 1 dogs. The ERP and AF/AT burden in group 2 remained unchanged between operations.

CONCLUSIONS Ablation of the head station GP between the ECANS and the ICANS prolonged the ERP acutely, but shortened regional ERPs and increased AF/AT burden chronically, suggesting that the ECANS may tonically inhibit the ICANS activity.

KEYWORDS Ablation; Atrial fibrillation; Autonomic nervous system; Ganglionated plexi; Proarrhythmia

ABBREVIATIONS **AF** = atrial fibrillation; **AT** = atrial tachycardia; **AV** = atrioventricular; **ECANS** = extrinsic cardiac autonomic nervous system; **ERP** = effective refractory period; **GP** = ganglionated plexi; **HFS** = high-frequency stimulation; **ICANS** = intrinsic cardiac autonomic nervous system; **PV** = pulmonary vein; **RAA** = right atrial appendage; **RIPV** = right inferior pulmonary vein; **RSPV** = right superior pulmonary vein; **SVC-Ao** = superior vena cava and aorta

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Introduction

Cardiac function is controlled by both the extrinsic and the intrinsic cardiac autonomic nervous system (ECANS and ICANS, respectively).[1,2] The former consists of the neurons in the brain stem nuclei, vagal trunks, chains of sympathetic ganglia along the spinal cord, and the postganglionic axons that course en route to the heart. The ICANS is composed of a neural network formed by axons and autonomic neurons concentrated at the ganglionated plexi (GP) embedded within epicardial fat pads. The ECANS and the ICANS operate dependently and also interdependently.[1,2] The GP located on the right pulmonary artery between the SVC and the aorta (SVC-Ao GP) was proposed to be the "head station" between the ECANS and the ICANS on the basis of observations that ablation of this GP acutely eliminated the effects of vagal stimulation on slowing the sinus rate and atrioventricular (AV) conduction.[3] That is, most of the efferent vagosympathetic fibers to the atria travel through this GP before innervating the heart.[3]

Clinical studies demonstrated a subgroup of patients with atrial fibrillation (AF) with rapid firing coming from

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nonpulmonary vein (PV) sites. It accounts for up to 20% of the AF cases, including those from the SVC.[4,5] While rapid focal firing from the PV often requires simultaneous activation of the sympathetic and parasympathetic components of the ICANS,[6–9] the mechanism underlying rapid firing of the SVC-atrial junction remains poorly understood. A recent study by Lu et al demonstrated that the SVC-Ao GP preferentially modulates the electrophysiological properties of the SVC-atrial junction, evidenced by the observation that the effective refractory period (ERP) was prolonged only at the SVC-atrial junction, but not other atrial or PV sites, when the SVC-Ao GP was ablated. Rapid focal firing from the SVC-atrial junction could be induced when high-frequency stimulation (HFS; 20 Hz) was delivered to the SVC-Ao GP, suggesting that a hyperactive state of the SVC-Ao GP may underlie the rapid firing from the SVC observed in patients with AF.[10] We hypothesized that the chronic effect of vagal denervation by ablating the SVC-Ao GP should reduce the AF burden by mitigating the vagal innervation of the heart.

Methods

Animal preparation

The protocol for the animal preparation was approved by the Committee for Experiments on Animals of the Taipei Veteran General Hospital. A total of 10 adult mongrel dogs (weighing 15–25 kg) were anesthetized with ketamine (10–20 mg/kg) and sodium pentobarbital (30 mg/kg intravenously). All animals received a warming blanket to maintain the core body temperature at 36.5 ± 1.5°C. The arterial blood gas was checked hourly to keep a balanced acid-base status (pH 7.35–7.45) and oxygenation ($SaO_2 > 90\%$ without hypercapnemia). All dogs were ventilated with room air by a positive pressure respirator. Oxygen was administered to maintain $SaO_2 > 90\%$. Venous access was obtained by using the Seldinger technique with an 8-F sheath from the right femoral vein. An arterial access was set up at the right femoral artery for blood pressure and body temperature monitoring and blood sampling. The chest was opened via a lateral thoracotomy at the fourth intercostal space, and the heart was exposed after an incision in the pericardium. The phrenic nerve was preserved during the incision. All electrograms recorded from the electrode catheter were amplified and digitally recorded by using a computer-based Bard Lab System (CR Bard Inc, Billerica, MA) filtered at 30–500 Hz.

All animals received 2 operations in this study. Because the SVC-Ao GP can be identified easily from right thoracotomy with a small incision and the damage is limited to the pericardium, the chest was opened through a right lateral thoracotomy at the fourth intercostal space in the first operation to minimize trauma and improve survival. Multielectrode catheters were sutured to multiple sites to obtain recordings and for stimulation at the right atrial appendage (RAA), right superior pulmonary vein (RSPV), and right inferior pulmonary vein (RIPV). A basket catheter introduced through the internal jugular vein was placed at the SVC-right atrial junction for recording SVC electrograms and stimulating the SVC-Ao GP. A single-chamber pacemaker (Medtronic) was placed in the right chest wall subcutaneously with an epicardial unipolar lead implanted in the RAA for recording the atrial event. The pacemaker was programmed to record the event of AF or atrial tachycardia (AT). The AF/AT episode onset was defined as the atrial rate above 300 beats/min for more than 5 seconds. Each event was also evaluated by the 2 investigators (L.W.L. and H.Y.C.) to exclude oversensing or noise artifact. Two temporary pacing wires were sutured at the right pulmonary venous-left atrial junction, and these pacing wires were fixed cutaneously at the skin of the right chest wall for checking atrial ERP weekly during the experiment. The second operation was done 10 weeks after the first operation. The chest was reopened through a right lateral thoracotomy. The placement of the multielectrode catheters and a basket catheter was similar to that in the first operation.

Identification and stimulation of the autonomic nervous system

The detailed preparation procedures have been reported before.[11] In brief, after the thoracotomy, the GPs were identified by applying HFS using a bipolar electrode probe though a Grass stimulator (20 Hz, 0.1 ms duration, square waves, 0.6–8.0 V). The fat pad containing the anterior right ganglionated plexus was situated between the caudal end of the sinoatrial node and the RSPV-atrial junction. The inferior right ganglionated plexus was located at the junction of the inferior vena cava and both atria. The SVC-Ao GP located at the interface between the SVC and the right pulmonary artery was identified by delivering HFS directly to the fat pad containing this GP from the epicardial side and to each spline of the basket catheter from the endocardial side.[10] A bradycardia response, which showed a progressive slowing of the sinus rate by 50% or the development of second- or third-degree AV block resulting from incremental voltage levels applied to the fat pad, was used as a surrogate marker for GP stimulation.

Programmed stimulation

The ERP was evaluated through the electrical programmed stimulation (pacing cycle length 300 ms) to multielectrode catheters and a basket catheter. Atrial tachyarrhythmia was defined as the irregular atrial beats (more than 300 beats/min for at least 5 seconds). The mean value of the ERP at the SVC sites was determined by averaging the ERPs acquired from 25 electrode pairs of the basket catheter.

Study protocols

First operation

In the first operation, ERPs were obtained from programmed stimulation at the RSPV, RIPV, RAA, and SVC. The ERPs of RSPV, RIPV, and RAA were also obtained during HFS at the SVC. In group 1 (n = 5), after verifying the location of