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The autonomic neural mechanism of right ventricular outflow tract tachycardia

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ABSTRACT

Background: Ventricular tachycardia (VT) and ventricular premature complexes (VPCs) originating from the right ventricular outflow tract (RVOT) are generally considered as benign arrhythmias, with ECG morphology showing LBBB pattern and inferior axis. Pathogenic mechanisms in the genesis of RVOT VT/VPC remain largely unknown. We aimed to investigate the neural mechanism in RVOT ventricular arrhythmias in canine model.

Methods: Twelve mongrel dogs (13.7 ± 1.3 kg, 5 male dogs) were studied through midline thoracotomies. High-frequency stimulation (HFS) was applied to the proximal pulmonary artery (PA) to induce RVOT VT/VPC. An EnSite Array and a mapping catheter were used for electroanatomical mapping. The RVOT and PA were surgically excised for immunohistochemistry studies, including tyrosine hydroxylase (TH) stain for sympathetic nerves and choline acetyltransferase (ChAT) stain for parasympathetic nerves.

Results: In nine (75%) out of twelve dogs, HFS of the proximal PA induced RVOT VT/VPC. The density of TH-positive nerves was significantly higher than that of ChAT-positive nerves (6803 ± 700 vs. 670 ± 252 $\mu m^2/mm^2$, $p < 0.001$). Furthermore, the density of TH-positive nerves was also significantly higher in the VT/VPC origin sites than that in the non-origin sites (18,044 ± 2866 vs. 5554 ± 565 $\mu m^2/mm^2$, $p = 0.002$). Catheter ablation of the proximal PA eliminated the inducibility of RVOT VT/VPC successfully.

Conclusions: HFS of the proximal PA could induce RVOT VT/VPC. The sympathetic nerves were densely innervated to the origin of RVOT VT/VPC, indicating the critical role of sympathetic hyperactivity in the initiation and perpetuation of RVOT VT/VPC.

1. Introduction

Ventricular tachycardia (VT) arising from the right ventricular outflow tract (RVOT) is one of the most common types of idiopathic ventricular arrhythmias (Nakagawa et al., 2002; Lerman et al., 2004). RVOT-VTs exhibit the following characteristics (Lerman et al., 2004; Cole et al., 2002): (1) they usually occur in patients without overt structural heart disease, (2) the surface 12-lead ECG typically shows left bundle branch block morphology and inferior axis, and (3) the tachycardia typically arises from a discrete area of the myocardium in the RVOT area.

Although pathogenic mechanisms in the genesis of RVOT-VT remained largely unknown, activation of sympathetic tone has been shown to play an important role in provoking as well as maintaining these arrhythmias. The frequency of ventricular arrhythmias is often increased during periods of wakefulness and activity, and they frequently disappear entirely during sleep (Lerman et al., 2004; Mont et al., 1991). They are sensitive to catecholamine infusion, and typically terminate in response to beta-blockers, calcium channel blockers, and adenosine (Iwai et al., 2006; Kim et al., 2007). Heart rate variability studies showed activation of sympathetic tone prior to the occurrence of these ventricular arrhythmias (Hayashi et al., 1997; Yoshida et al., 1998; Zimmermann, 2005).

Sympathetic fibers of the ventromedial cardiac nerve (VMCN) and branches of ventrolateral cardiac nerve (VLCN) innervate the myocardium within the proximal pulmonary artery (PA) and the RVOT (Randall et al., 1972). Recently, an animal model has been described for RVOT tachycardias by high-frequency stimulation (HFS) of the

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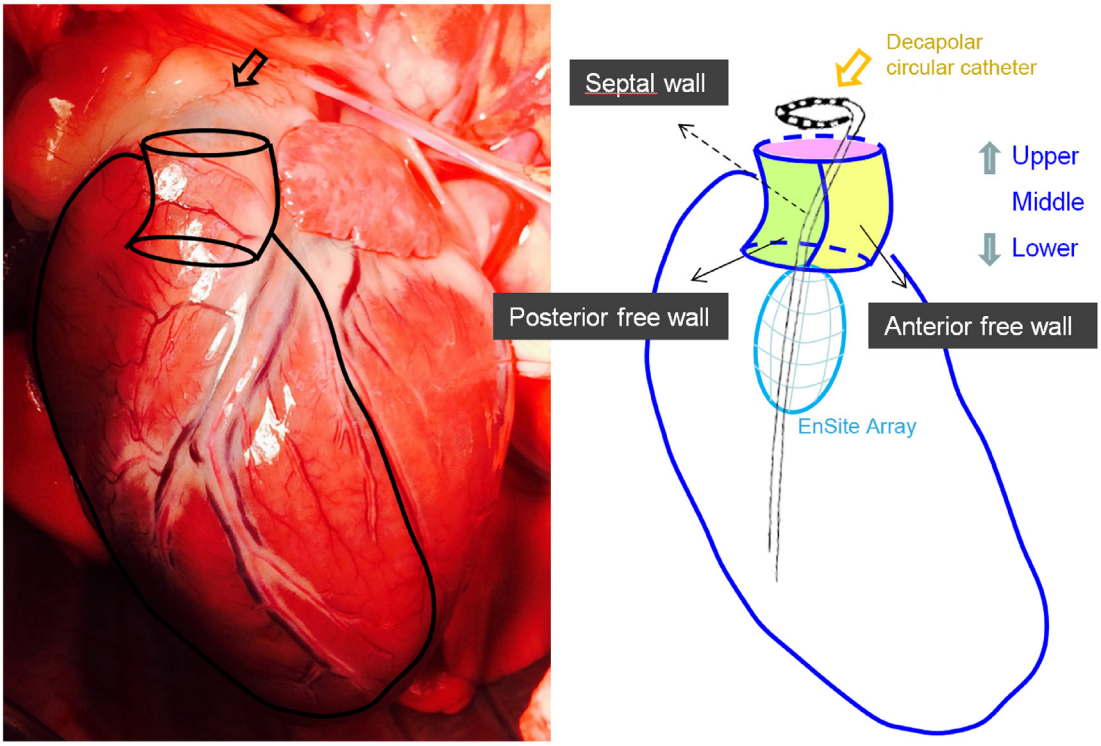

Fig. 1. Canine heart and the locations of the decapolar circular catheter and the EnSite Array. Right ventricular outflow tract was divided into 9 parts for tissue sampling and immunohistochemistry study: upper/middle/lower parts of anterior free wall/posterior free wall and septal wall.

extravascular sympathetic nerves within the PA innervating the RVOT (Zhou et al., 2006). Similarly, HFS in the left pulmonary artery successfully induced RVOT-ventricular premature complexes (VPCs) and/or VT in a human model (Hasdemir et al., 2009). However, in both models, the mechanism whereby a discrete area of myocardium in the RVOT becomes arrhythmogenic is yet to be clarified. Thus, the aim of this study was to investigate the neural mechanism of RVOT ventricular arrhythmias by using HFS within the PA in adult mongrel canine model.

2. Material and methods

2.1. Animal preparation

The protocol for this study was approved by the Committee for Experiments on Animals of the Taipei Veteran General Hospital. The details were described in previous publications (Yamada et al., 2017; Chang et al., 2016; Lo et al., 2016). A total of twelve adult mongrel dogs (weight 15–25 kg) were anesthetized with ketamine (10–20 mg/kg) and sodium pentobarbital (30 mg/kg intravenous). No intervention is performed before experimental protocols in these dogs. 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 hypercapnia). All dogs were ventilated with room air with a positive pressure respirator. Oxygen was administered to maintain SaO_2 > 90%. Venous access was obtained by using the Seldinger technique from the femoral veins. An arterial access was set up at the right femoral artery for body temperature monitoring and blood sampling. The chest was opened via a mid-sternal thoracotomy and the heart was exposed after an incision through the pericardium.

2.2. Electroanatomic mapping, signal recording and analysis during sinus rhythm

The electroanatomic mapping was performed using a noncontact mapping system (NavX, St. Jude, MN, USA), consisted of a 9-French catheter with a multielectrode array (MEA) surrounding a 7.5-mL balloon mounted at the distal end. The detail has been described in our previous manuscript (Chang et al., 2016; Lo et al., 2011). In brief, the MEA catheter was placed into the right ventricle via right or left femoral vein. The system located the three-dimensional position of the electrodes on any desired catheter relative to the MEA using a navigation signal. Navigation provided the means to define a model of the chamber anatomy and to track the position of a standard contact catheter within the chamber relative to labeled points of interest. Over 3000 simultaneous virtual unipolar electrograms were mathematically reconstructed and displayed on the anatomical model, producing isopotential or isochronal color maps. Continuous recording of the RVOT global signals was obtained during the sinus rhythm. Raw data detected by the MEA was amplified and digitally transferred to a computer workstation.

A 4-mm-tip catheter was inserted into the right ventricle and was also used to collect right ventricular geometric boundary and local bipolar ventricular signals during sinus rhythm with a point-by-point approach. All bipolar signals suitable for the frequency analysis and electrogram morphology analysis were exported for analysis. This catheter was then removed after the collection right ventricular anatomy and electrical signals of sinus rhythm.

2.3. Induction and identification of RVOT VT or ectopy

A quadripolar catheter was positioned in the right atrial appendage, and another 5-French decapolar circular catheter was positioned in the PA so as to contact the endovascular circumference of the PA. Before the induction of RVOT ventricular arrhythmias by HFS, all catheters were put in place without manipulation, and the electrocardiography should show sinus rhythm without any spontaneous VPC. A 50-msec train of high frequency electrical stimulation with 200 Hz and 0.1 msec pulse duration (Grass Stimulator, S-88, Astro-Med Industrial Park, West Warwick, RI, USA) was applied at each of the bipolar pair of the circular