Effects of ganglionated plexi ablation on ventricular electrophysiological properties in normal hearts and after acute myocardial ischemia

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**Abstract**

**Background:** Ganglionated plexi (GP) ablation has been shown to play an important role in atrial fibrillation (AF) initiation and maintenance. Also, GP ablation increases chances for prevention of AF recurrence. This study investigated the effects of GP ablation on ventricular electrophysiological properties in normal dog hearts and after acute myocardial ischemia (AMI).

**Methods:** Fifty anesthetized dogs were assigned into normal heart group (n=16) and AMI heart group (n=34). Ventricular dynamic restitution, effective refractory period (ERP), electrical alternans and ventricular fibrillation threshold (VFT) were measured before and after GP ablation in the normal heart group. In the AMI heart group, the incidence of ventricular arrhythmias and VFT were determined.

**Results:** In the normal heart group, GP ablation significantly prolonged ERP, facilitated electrical alternans but did not increase ERP dispersion, the slope of restitution curves and its spatial dispersion. Also, GP ablation did not cause significant change of VFT. In the AMI heart group, the incidence of ventricular arrhythmias after GP ablation was significantly higher than that in the control group or the GP plus stellate ganglion (SG) ablation group (P<0.05). Spontaneous VF occurred in 8/12, 1/10 and 2/12 dogs in the GP ablation group, the GP plus SG ablation group and the control group, respectively (P<0.05). VFT in the GP ablation group showed a decreased trend though a significant difference was not achieved compared with the control or the GP plus SG ablation group.

**Conclusions:** GP ablation increases the risk of ventricular arrhythmias in the AMI heart compared to the normal heart.

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1. Introduction

Recently, basic and clinical studies have revealed the critical contribution of the intrinsic cardiac autonomic nervous system (ICANS) in atrial fibrillation (AF) initiation and maintenance [1–8]. Ganglionated plexi (GP) within epicardial fat pad serves as the most important component in the ICANS [9–12]. GP ablation has been shown to increase the success rate of AF ablation, particularly in addition to pulmonary vein isolation procedures [5–7,13].

Although considerable evidence has confirmed the efficacy of GP ablation for the prevention of AF, the effects of GP ablation on ventricular electrophysiological properties remain unknown. It is well known that cardiac autonomic modulation significantly influences the initiation of ventricular arrhythmias (VA) and sudden cardiac death. An increase in parasympathetic activity or a reduction in sympathetic activity significantly decreases the susceptibility of the heart to ventricular fibrillation (VF), while an enhancement of sympathetic activity or an impairment of parasympathetic activity increases it [14,15]. As cell bodies of parasympathetic postganglionic neurons innervating the heart are mainly located on the atrial GP, destruction of cardiac autonomic innervation at the atria may also damage ventricular autonomic innervation [9–11].

Recently, Osman et al. [16] reported a case of a patient with AF undergoing pulmonary vein isolation with a profound vagal response, subsequently developed VF after programmed ventricular stimulation. Thus, we hypothesized that destruction of the major cardiac parasympathetic elements by GP ablation might predispose the heart to VA. In the present...
study, we investigated the effects of GP ablation on ventricular electrophysiological properties in normal dog hearts and after acute myocardial ischemia (AMI).

2. Methods

2.1. Animal preparation

All animal studies were reviewed and approved by the animal experimental administration of Wuhan University, China. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the United States National Institutes of Health (NIH Publication No. 85-23, revised 1996). Fifty adult mongrel dogs weighing 18–25 kg were randomly assigned into a normal heart group (n = 16) which consisted of 8 dogs without GP ablation and 8 dogs with GP ablation and an AMI heart group (n = 18) which consisted of 12 dogs without GP ablation, 12 dogs with GP ablation and 10 dogs with GP plus stellate ganglion (SG) ablation. All dogs were anesthetized with 30 mg/kg Na-pentobarbital and ventilated with room air by a positive pressure ventilator. Additional maintenance doses of 2 mg/kg Na-pentobarbital were administered at the end of each hour during the procedure. Systemic arterial pressure was monitored during the whole procedure using a computer-based Lab System (Lead 2000B, Jingjiang Inc., China). A heating pad was used to maintain the core body temperature of the dogs at 36.5 ± 1.5 °C.

2.2. GP ablation

High-frequency electrical stimulation (20 Hz, 0.1 ms duration, 0.6–5 V) was applied to identify the 4 major GP [1,2]: (1) anterior right GP located at the right superior pulmonary vein–atrial junction; (2) inferior right GP located at the junction of inferior vena cava and both atria; (3) superior left GP located adjacent to the left superior pulmonary vein–atrial junction between the left atrial appendage and left pulmonary artery; and (4) inferior left GP located at the left inferior pulmonary vein–atrial junction. An irrigated large-tip (3.5 mm) electrode catheter (Biosense-Webster Inc. Diamond Bar, CA, USA) was used for ablation. Radiofrequency current (<35 W) was immediately delivered to the sites showing sinus rate slowing or atrioventricular conduction block during high-frequency electrical stimulation. Complete ablation was verified by elimination of sinus rate slowing or atrioventricular conduction block when applying maximal strength of stimulation to the ablated area. We also ablated the ligament of Marshall which is also richly innervated by both sympathetic and parasympathetic neural elements and serves as an important part of ICANS.

2.3. SG ablation

After a left or right thoracotomy was performed, high-frequency electrical stimulation (20 Hz, 0.1 ms duration, 30–50 V) was applied to identify the left or right stellate ganglion. Ablation was considered complete when stimulation of each ablated ganglion no longer produced any changes of heart rate and/or blood pressure. The ablation procedure was the same as that of GP ablation.

2.4. Cardiac electrical recording

Both left and right thoracotomies were performed at the 5th intercostal space to expose the heart. Two multi-electrode catheters with 2 mm interelectrode distance were sutured to record electrogram at 8 epicardial sites from the apex to the base in the left and right ventricular free walls (Fig. 1). A custom-made Ag-AgCl electrode was used to record monophasic action potentials (AP) from the epicardial surface of the left and right ventricular free walls (Figs. 1, 2A) at 6 sites: left ventricular apex (LVA), left ventricular base (LVB), the median area between LVA and LVB (LVM), right ventricular apex (RVA), right ventricular base (RVB), and the median area between RVA and RVB (RVM). Standard surface electrocardiograms (leads I, II, III, aVF, aVR, AVL, and aVF, Fig. 1C) were continuously monitored. A computer-based Lab System (Lead 2000B, Jingjiang Inc., China) was used to display all recordings and to perform all pacing protocols. The monophasic APs were filtered at 0.05 to 1200 Hz and local cardiac electrograms between 30 and 500 Hz.

2.5. Stimulation protocol

Ventricular pacing was performed to determine the effective refractory period (ERP) of the ventricular myocardium. The ventricular ERP was determined using an 8-beat drive train (S1, 300 ms cycle length) followed by an extrastimulus (S2) and repeated 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. ERP dispersion was defined as the coefficient of variation (CV, standard deviation/mean) of the ERP at all 8 sites. A dynamic steady state pacing protocol (S1S1) with a series of pulse trains at constant pacing cycle length [17,18] was performed to obtain monophasic AP duration (APD) of each site (Fig. 2B). The distal pair of the electrodes attaching to the left or right ventricular apex was used for pacing at twice the diastolic threshold. The pulse train was delivered at an initial cycle length just slightly shorter than the sinus cycle length and then repeated with progressively shorter cycle length in an initial stepwise fashion by 20 or 30 ms and a subsequent stepwise fashion by 10 ms until APD alternans occurred (Fig. 2C). Each pulse train was maintained for 30 s to achieve a steady state. After each pulse train was delivered, the pacing was interrupted for 2 min to minimize the pacing memory effects.

Fig. 1. Schematic representation and catheter positions in the left (A) and right (B) ventricular free walls and simultaneous surface and intracardiac electrocardiogram recording (C). I, II, III, aVR, aVL and aVF are surface electrocardiogram leads. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; LAA, left atrial appendage; RAA, right atrial appendage; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; PAT, pulmonary artery trunk; SVC, superior vena cava; IVC, inferior vena cava; LVA, left ventricular apex; LVB, left ventricular base; LVM, the median area between LVA and LVB; RVA, right ventricular apex; RVB, right ventricular base; RVM, the median area between RVA and RVB.

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2. The maximum slope ($S_{\text{max}}$) of each restitution curve was determined at the
$$\beta = \alpha \cdot e^{-\frac{T}{\tau}}$$
3.1. Effect of GP ablation on ventricular ERP and APD in the normal heart

Table 1 summarizes ventricular ERP at 8 epicardial sites in GP ablation group in the normal heart. Both left and right ventricular ERP

$$y = \alpha - \beta e^{-\frac{\tau}{\tau}}$$

3. Results

2.8. Measurement of VF threshold (VFT)

The VFT in normal hearts was determined in 8 dogs in each group. However, among the dogs with AMI in each group, the VFT was determined in the dogs without spontaneous VF after 1 h of recording. To eliminate variations of vulnerability to fibrillation associated with the slowing or acceleration of heart rate, all VFT measurements were performed at the same heart rate. At the end of a 20 beat drive train with a pacing cycle length of 300 ms, 100 ms S1-S1 stimuli were applied to the RVA with an increase of stimuli intensity steps of 2 V until VF was induced. Each stimulus lasted for 10 s and interrupted by a 30-second rest period before next test. VFT was defined as the minimum voltage required to produce sustained VF.

2.9. Statistical analysis

All continuous variables were expressed as mean ± standard deviation. The mean ERP and VFT acquired before and after GP ablation were compared using a paired-samples t-test. The number of VA events and the duration of VT acquired during coronary artery ligation were compared using an independent-samples t-test. The nonparametric Wilcoxon signed ranks test was applied for comparisons of the APD alternans cycle length before and after GP ablation. The incidence of VF was compared by the Fisher's exact test. SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Statistical significance was defined as $P < 0.05$.

Before GP ablation After GP ablation

<table>
<thead>
<tr>
<th>Site</th>
<th>Before GP ablation</th>
<th>After GP ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV1</td>
<td>165.8 ± 17.8</td>
<td>185.0 ± 20.2*</td>
</tr>
<tr>
<td>LV2</td>
<td>157.5 ± 16.6</td>
<td>175.0 ± 20.7*</td>
</tr>
<tr>
<td>LV3</td>
<td>159.2 ± 19.3</td>
<td>179.2 ± 23.9*</td>
</tr>
<tr>
<td>LV4</td>
<td>158.3 ± 14.7</td>
<td>160.0 ± 21.7*</td>
</tr>
<tr>
<td>RV1</td>
<td>165.0 ± 23.5</td>
<td>184.2 ± 26.8*</td>
</tr>
<tr>
<td>RV2</td>
<td>163.1 ± 22.3</td>
<td>180.8 ± 25.7*</td>
</tr>
<tr>
<td>RV3</td>
<td>157.5 ± 14.2</td>
<td>175.8 ± 18.3*</td>
</tr>
<tr>
<td>RV4</td>
<td>159.2 ± 21.1</td>
<td>173.3 ± 20.2*</td>
</tr>
</tbody>
</table>

Four different sites from the apex (LV1 and RV1) to the base (LV4 and RV4) of the left and right ventricular free walls were recorded. LV, left ventricle; RV, right ventricle.

* $P < 0.05$ when compared with the values before GP ablation.

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2.6. Construction of APD restitution curves

For construction of the APD restitution curve, we measured APD$_{90}$ (an APD at 90% repolarization) and diastolic interval (DI) at the baseline and at each pacing cycle length for each site by Lead 2000 Lab System. Each DI was calculated from the end of repolarization time of the prior beat to the beginning of the AP upstroke of the current beat (Fig. 2A). The dynamic APD restitution curves were constructed from (DI, APD$_{90}$) pairs using Origin 7.5 (OriginLab, Co., Northampton, MA, USA) as previously described [19]. Briefly, an exponential curve (Equality 1) using the Levenberg-Marquardt method was used for this analysis. With each $\beta$ and $\tau$ and DI, the slope was calculated using Equality 2. The maximum slope ($S_{\text{max}}$) of each restitution curve was determined at the shortest DI. The spatial dispersion of the $S_{\text{max}}$ of the APD restitution curve was determined by calculating the CV of $S_{\text{max}}$ among the 6 recording sites.

$$\text{slope} = \frac{-\beta}{\tau} \cdot e^{-\frac{T}{\tau}}$$

2.7. Induction of AMI and measurement of VA incidence

When the stimulation protocol was finished, AMI was induced by ligating the proximal left anterior descending coronary artery in 12 dogs in the control and GP ablation groups and in 10 dogs in the GP plus SG ablation group. Electrocardiograms were continuously monitored for 1 h to record the incidence and duration of VA including ventricular premature contraction (VPC), ventricular tachycardia (VT) and VF.

2.8. Measurement of VF threshold (VFT)

The VFT in normal hearts was determined in 8 dogs in each group. The cycle length at which APD alternans occurred was recorded. The same dynamic pacing protocol was performed at LVA or RVA to obtain the APD of the sites of LVA, LVB, LVM, RVA, RVB and RVM before and after GP ablation. The sites where monophasic AP was recorded were marked to make sure that protocols could be repeated at the same sites after GP ablation.

before the next pacing train. The cycle length at which APD alternans occurred was recorded. The same dynamic pacing protocol was performed at LVA or RVA to obtain the APD of the sites of LVA, LVB, LVM, RVA, RVB and RVM before and after GP ablation. The sites where monophasic AP was recorded were marked to make sure that protocols could be repeated at the same sites after GP ablation.

$$y = \alpha - \beta e^{-\frac{T}{\tau}}$$

$$\text{slope} = \frac{-\beta}{\tau} \cdot e^{-\frac{T}{\tau}}$$

Fig. 2. The monophasic action potential recordings at left ventricular apex during sinus rhythm and dynamic pacing from an ablated dog. (A) The action potential recordings during sinus rhythm showing the calculation of diastolic interval (DI) and measurement of action potential duration at 90% repolarization (APD$_{90}$). The cycle length is 375 ms. (B) The action potential recordings during pacing at a cycle length of 250 ms without APD alternans. (C) APD alternans occurred during pacing at a cycle length of 200 ms. Both morphology alternans (solid and dashed arrows in left panel) and duration alternans (numbers in right panel) are shown. The numbers in the right panels represent APD (ms). CL, cycle length; PCL, pacing cycle length.
were significantly prolonged by GP ablation when compared with baseline values. However, GP ablation did not increase the ERP dispersion as measured by CV-ERP (Fig. 3A).

Correspondingly, the mean APD90 at each recording site was also significantly increased by GP ablation (Table 2). However, GP ablation did not increase the spatial dispersion of the APD90 (CV-APD90, Fig. 3B) when compared with baseline.

3.2. Effect of GP ablation on ventricular APD restitution in the normal heart

Fig. 4 is a typical example showing the effect of GP ablation on ventricular APD restitution curves in the normal heart at the 6 epicardial sites: LVA, LVB, LVM, RVA, RVB and RVM. GP ablation caused an upward shift of the curve and a prolongation of the APD90 when compared with baseline at corresponding DI. For example, the APD90 in the LVA was increased from a baseline of 245 ms to 265 ms after GP ablation at the same DI of 150 ms. The mean Smax was <1 at each site after GP ablation, similar to baseline (Table 2). Meanwhile, GP ablation did not increase the spatial dispersion of the Smax (CV-Smax, Fig. 3C) when compared with baseline.

3.3. Effect of GP ablation on APD alternans in the normal heart

Fig. 5 shows the pacing cycle length at which APD alternans occurred before and after GP ablation in the normal heart. Compared with the baseline state, APD alternans occurred at significantly longer cycle lengths after GP ablation at each site.

3.4. Effect of GP ablation on VA incidence in the AMI heart

As shown in Table 3, after AMI was induced by ligation of the proximal left anterior descending coronary artery, 1 h of continuous electrocardiogram recording showed that the number of episodes of VPC in GP ablation group was significantly increased when compared with that in the control group and in the GP plus SG ablation group. The mean duration of VT was longer and the occurrence of spontaneous VF was higher in GP ablation group when compared with the other groups. Most of VF episodes occurred at 5 to 15 min after coronary artery ligation, while 2 dogs in GP ablation group manifested VF within 2 min and another 2 dogs showed VF at more than 30 min later. Once VF occurred, no intervention was adopted to terminate VF. No VF episode converted to VT and stopped spontaneously. All the dogs in whom VF occurred, died.

3.5. Effect of GP ablation on VFT in the normal and AMI hearts

Table 4 summarizes the VFT in the normal and AMI hearts. In the normal heart, VFT measurements were accomplished in 8 dogs in each group and there was no statistical significance in VFT between GP ablation and control groups. In dogs with AMI, 4 of 12 dogs with GP ablation, 9 of 10 dogs with GP plus SG ablation and 10 of 12 dogs without GP ablation survived for 1 h to be subjects for subsequent measurement of VFT. VFTs in the GP ablation group and the control group were significantly decreased compared with that in the normal heart. For comparison between groups, VFT in GP ablation group showed a decreased trend though a significant difference was not achieved when compared with control group (P=0.093) or GP plus SG ablation group (P=0.084).

4. Discussion

The present study showed that 1) in normal hearts, GP ablation prolonged ventricular ERP and APD but did not increase their spatial dispersion. GP ablation facilitated the occurrence of APD alternans but did not change VFT and did not increase the slope of the APD restitution curve.

Table 2

<table>
<thead>
<tr>
<th>Smax</th>
<th>Before GP ablation</th>
<th>After GP ablation</th>
<th>Before GP ablation</th>
<th>After GP ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVA</td>
<td>0.94±0.24</td>
<td>0.90±0.18</td>
<td>219.3±13.9</td>
<td>257.5±15.7*</td>
</tr>
<tr>
<td>LVM</td>
<td>0.76±0.20</td>
<td>0.78±0.20</td>
<td>216.7±12.0</td>
<td>256.9±12.3*</td>
</tr>
<tr>
<td>LVB</td>
<td>0.86±0.24</td>
<td>0.82±0.21</td>
<td>213.8±9.0</td>
<td>254.1±14.1*</td>
</tr>
<tr>
<td>RVA</td>
<td>0.88±0.29</td>
<td>0.90±0.27</td>
<td>216.7±12.7</td>
<td>255.8±12.2*</td>
</tr>
<tr>
<td>RVM</td>
<td>0.81±0.19</td>
<td>0.78±0.17</td>
<td>213.8±11.5</td>
<td>254.3±9.5*</td>
</tr>
<tr>
<td>RVB</td>
<td>0.72±0.17</td>
<td>0.77±0.18</td>
<td>214.1±8.3</td>
<td>253.8±8.8*</td>
</tr>
</tbody>
</table>

The data of Smax were obtained from dynamic restitution curves and the data of APD90 were obtained from baseline state before GP ablation (cardiac cycle length 416.4±41.2 ms) and after GP ablation (cardiac cycle length 402.8±46.2 ms, P>0.05). LVA, left ventricular apex; LVB, left ventricular base; LVM, the median area between LVA and LVB; RVA, right ventricular apex; RVM, the median area between RVA and RVB. 

* P<0.05 when compared with the values of APD90 before GP ablation.
restitution curve and the spatial dispersion of S\textsubscript{max}; 2) in AMI hearts, GP ablation significantly promoted the occurrence of VA while SG ablation attenuated this susceptibility.

4.1. Effect of GP ablation on ventricular ERP and APD

It has been shown that parasympathetic activation by vagus nerve stimulation causes ventricular ERP and APD prolongation\([15,20]\). We also determined that GP activation by electrical stimulation can prolong ventricular ERP and APD (the data was not shown in the present study), indicating that GP regulate ventricular electrophysiological properties. It can be argued that ventricular ERP and APD should be shortened not prolonged after GP ablation as GP stimulation prolongs it. However, just like stellate ganglionectomy causes ventricular APD shortening\([21]\), ERP prolongation induced by GP ablation may still happen. Several reasons may be useful to explain the ERP and APD

Fig. 4. Typical examples of dynamic APD restitution curves before and after GP ablation in one dog. The APD restitution curves were shifted upward by GP ablation. All the other abbreviations are identical to Fig. 1.

Fig. 5. The APD alternans pacing cycle lengths at each site of the left (A) and right (B) ventricular free walls before and after GP ablation. See text for further details. All the other abbreviations are identical to Fig. 1.

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prolongation in the present study. First, accentuated antagonism between sympathetic and parasympathetic autonomic nervous system may be one of the mechanisms. Although it seems that sympathetic and parasympathetic nerves antagonize to each other, removing one of the two may not directly increase the other’s effect. Second, GP ablation destroyed not only parasympathetic neurons but also sympathetic neurons that control the heart. Third, as GP has a complex neurochemical anatomy [22], GP ablation may cause expression alterations or malfunctions of some receptors and ion channel proteins on ventricular myocardium which may be related to the changes in ventricular ERP and APD. Further investigations on the detailed mechanisms by which GP ablation prolongs ventricular ERP and APD are warranted.

4.2. APD restitution slope and VA

The APD restitution hypothesis [23–26] asserts that a steep restitution slope (>1) promotes while a flattened restitution slope (<1) prevents the initiation and maintenance of VF. In other words, steep restitution curves more readily cause conduction block and wave breakup, two important factors for VF initiation and maintenance. In our study, GP ablation did not increase the slope of the APD restitution curve (mean S\text{max} < 1) in the normal heart and the VFT in the GP-ablated heart was also similar to baseline, suggesting that GP ablation did not increase the propensity for VF in normal hearts. In addition, it is known that a greater spatial dispersion of APD restitution kinetics may cause an easier initiation and maintenance of cardiac fibrillation [27–29]. In this study, GP ablation did not increase the spatial dispersion of the S\text{max}, also demonstrating that GP ablation in normal hearts may not predispose to VF.

4.3. APD alternans and VA

According to the classic hypothesis of APD restitution, APD alternans is a predictor of VF or sudden cardiac death which occurs more easily when the slope of the APD restitution curve is >1 [23–26]. However, recent studies showed that APD alternans can also occur even though the APD restitution slope is still <1 if the coupling between intracellular calcium and cellular membrane voltage is positive, because the instability of intracellular calcium can also synergistically promote alternans [30,31]. This alternans is usually electromechanically concordant and less-arrhythmogenic [31]. In our study, although the slope of the APD restitution curve in GP-ablated hearts was <1 (Table 2), APD alternans occurred at longer pacing cycle length when compared with baseline. We presumed that the alternans in our study may be concordant.

However, the detailed mechanism by which GP ablation facilitated the occurrence of APD alternans requires further investigation.

4.4. ERP dispersion and VA

The spatial dispersion of refractoriness hypothesis [32,33] posits that a large spatial dispersion of refractoriness facilitates the occurrence of conduction block, promoting reentry and the initiation of and maintenance of VF. According to this hypothesis, VF can be maintained in regions with large gradients of refractoriness caused by preexisting electrophysiological heterogeneities. In the normal ventricle, ERP dispersion exists presumably due to gross anatomical structure such as subepicardial vessels or regional differences in ionic currents, as suggested by studies in isolated guinea pig heart which shows that APDs increased consistently from the ventricular apex to the base with gradients in k\text{c} [34] or k\text{cl} [35] orienting approximately in the same direction. The ERPs in our study, however, roughly exhibited an apical to basal shortening. Species differences or differences between in vivo working hearts and isolated hearts may explain the different results. Although tissue damage or pathological conditions can enhance dispersion of refractoriness and produce a functional arc of conduction block, GP ablation in our study prolonged ventricular ERP but did not cause a significant increase of ERP dispersion (Fig. 3A), indicating a low risk of VF. We presume that the alteration of tissue heterogeneity induced by GP ablation may be insufficient to cause a significant increase of ERP spatial dispersion and conduction block.

4.5. GP ablation and VA incidence in the AMI heart

AMI always results in electrical instability that leads to life-threatening cardiac arrhythmias [36,37]. VF is the most common fatal arrhythmia during AMI which can be the result of a rapid increase in sympathetic activity [38–40]. It has been known as a general rule that parasympathetic effects are protective for ventricular arrhythmogenesis while impaired parasympathetic control of the heart will increase the susceptibility to lethal VA. A previous study has confirmed that direct stimulation of the vagus can prevent VF during acute ischemia in dogs susceptible to sudden cardiac death [41]. As atrial GP contain most of the cell bodies of parasympathetic postsynaptic neurons innervating the heart, GP ablation may dramatically reduce the parasympathetic control of the heart, indirectly increasing sympathetic activity. Of note, although GP ablation may cause an increase in sympathetic activity due to the impaired parasympathetic control of the heart, it may not be arrhythmogenic in the normal heart due to the lack of an appropriate substrate for VA as shown in our study. However, AMI could provide the necessary substrate and/or trigger activity (VPCs) for lethal VA. In the present study, the incidence of VA was significantly increased and the VF was significantly facilitated in dogs with GP ablation when compared with the dogs without GP ablation. However, the occurrence of VA in GP-ablated dogs was attenuated by SG ablation. These results suggested that ICANS is a complex neural network whereas destruction of the mainly parasympathetic component of the ICANS may result in an imbalance of neural regulation for the heart, thereby promoting the genesis of fatal arrhythmias.

4.6. Clinical implications

It has been demonstrated by basic and clinical studies that GP play an important role in AF initiation and maintenance [1–8]. Recent studies also demonstrated that GP ablation can increase the success rate of AF ablation which includes pulmonary vein isolation procedures [5–7,13]. Furthermore, it has been reported that an AF patient undergoing pulmonary vein isolation developed VF during programmed ventricular stimulation [16], which causes concern as to the safety of GP ablation in specific AF patients. Based on the spatial dispersion of refractoriness hypothesis and the APD restitution hypothesis, our study demonstrated

<table>
<thead>
<tr>
<th>Table 3</th>
<th>The occurrence of VA episodes in each group during 1 h recording.</th>
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<tbody>
<tr>
<td></td>
<td>Control group (n = 12)</td>
</tr>
<tr>
<td>VPC episodes</td>
<td>94 ± 92</td>
</tr>
<tr>
<td>VT episodes (duration, s)</td>
<td>4 (1.5 ± 0.7)</td>
</tr>
<tr>
<td>Spontaneous VF episodes (%)</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

* P < 0.05 when compared with control group or GP plus SG ablation group.

As 4 dogs in this group underwent VF within 5 min after coronary artery ligation, VPC episodes were calculated only from 8 dogs.

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that GP ablation did not increase the spatial dispersion of ventricular ERP and the slope of APD restitution curve in normal canine hearts, indicating that GP ablation may not increase the risk of VA in AF patients with structurally normal hearts. However, our study showed that GP ablation facilitated VF and increased the occurrence of VA in dogs undergoing AMI, providing the implication that in patients with structural heart disease such as coronary artery disease and ischemic heart disease, GP ablation might increase the risk of VA.

4.7. Study limitations

There were several limitations in our study. Firstly, although we investigated the effect of GP ablation on ventricular electrophysiological properties in AMI hearts, further study will be needed to confirm whether the acquired results can be applied to chronic myocardial infarction hearts or the hearts in the chronic phase of stable obstructive coronary artery disease without ischemia. Secondly, the ERP, APD or restitution properties were not investigated in the acute phase of myocardial ischemia because we focused on the spontaneous VA in the AMI dogs. Therefore, the data in the present study was not sufficient to explain why VA was seen more frequently in AMI dogs with GP ablation. Further study will be needed to clarify the exact mechanisms. Thirdly, we only investigated the acute effect of GP ablation on ventricular electrophysiological properties; medium and long term effects were not determined. Fourthly, since we only performed GP ablation epicardially in our study, whether the results might be applicable to endocardial GP ablation remains to be elucidated by further studies. Lastly, we did not directly record sympathetic activity in our study to test whether GP ablation induced an increase of cardiac sympathetic activity. However, we verified that SC ablation prevented the occurrence of VA after GP ablation, indirectly supporting that increased cardiac sympathetic tone may serve as one of the mechanisms.

5. Conclusions

GP ablation prolonged the ventricular ERP, facilitated the APD alternans but did not change the VFT and did not increase the slope of the restitution curves and the spatial dispersions of ERP and S_max in normal hearts. However, GP ablation significantly increased the incidence of VA and facilitated spontaneous VF in AMI hearts which may be in part due to imbalances within the ICANS.

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