Atrial fibrillation (AF) is the most common sustained arrhythmia, and the autonomic nervous system plays an important role in its initiation and maintenance. 1–3 Previous studies have shown that the cardiac autonomic nervous system forms an interconnected neural network composed of multiple ganglionated plexi (GP) and the ligament of Marshall (LOM); this network modulates and controls the release of neurotransmitters within the myocardium.3 There are 4 major GP within epicardial fat pads: (1) the anterior right GP, situated in the fat pad near the base of the right pulmonary veins and adjacent to the caudal end of the sinoatrial node; (2) the inferior right GP, located in the fat pad close to the junction of the inferior vena cava and both atria; (3) the superior left GP, situated in the fat pad between the left superior pulmonary vein–atrial junction and left pulmonary artery; and (4) the inferior left GP, located in the fat pad at the left inferior pulmonary vein–atrial junction.2 Multiple investigations have found that systematic epicardial GP ablation could increase the acute success rate of radiofrequency ablation for AF in patients or canine models,1–6 whereas partial denervation showed controversial results in long-term follow-up.7–10 Therefore, whether systematic epicardial GP ablation could enhance AF ablation in the long term has not been fully clarified.

In addition, previous investigations have shown that augmented sympathetic tone may increase the vulnerability of ventricular tachyarrhythmias, whereas increased vagal activity has a protective effect on ventricular tachyarrhythmias.11 However, whether atrial denervation can affect ventricular innervation and predispose the heart to ventricular tachyarrhythmias has not been determined.

Therefore, the purposes of the present study were to (1) investigate the long-term electrophysiological outcomes of systematic epicardial GP ablation in the atrium and ventricle in dogs and (2) evaluate the properties of neural remodeling in the atrium and ventricle after systematic epicardial GP ablation.

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Original Article

Ablation of Epicardial Ganglionated Plexi Increases Atrial Vulnerability to Arrhythmias in Dogs

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Background—Previous studies have suggested that systematic ablation of ganglionated plexi (GP) could increase the short-term success rate of radiofrequency ablation for atrial fibrillation, but the long-term efficacy of this approach is not fully established.

Methods and Results—Twenty-four mongrel dogs were divided into 3 groups: epicardial GP ablation group 1 (n=8), epicardial GP ablation group 2 (n=8), and a sham operation group (n=8). In the 2 epicardial GP ablation groups, the 4 major GP and the ligament of Marshall were systematically ablated. The effective refractory period and inducibility of tachyarrhythmias were measured before and immediately after GP ablation in epicardial GP ablation group 1 and 8 weeks later in the other 2 groups. Tyrosine hydroxylase and choline acetyltransferase expressions were also determined immunohistochemically 8 weeks later in the latter groups. Compared with epicardial GP ablation group 1 and the sham operation group, epicardial GP ablation group 2 had the shortest atrial and ventricular effective refractory period and the highest inducibility of atrial tachyarrhythmias. The inducibility of ventricular tachyarrhythmias among the 3 groups was comparable. The density of tyrosine hydroxylase– and choline acetyltransferase–positive nerves in the atrium was the highest in epicardial GP group 2, whereas there were no significant intergroup differences in the densities of these 2 types of nerves in the ventricle.

Conclusions—After 8 weeks of healing, epicardial GP ablation without additional atrial ablation was potentially proarrhythmic, which may be attributable to decreased atrial effective refractory period and hyper-reinnervation involving both sympathetic and parasympathetic nerves. (Circ Arrhythm Electrophysiol. 2014;7:711-717.)

Key Words: atrial fibrillation • autonomic nervous system • catheter ablation • denervation • remodeling

Atrial fibrillation (AF) is the most common sustained arrhythmia, and the autonomic nervous system plays an important role in its initiation and maintenance.1–3 Previous studies have shown that the cardiac autonomic nervous system forms an interconnected neural network composed of multiple ganglionated plexi (GP) and the ligament of Marshall (LOM); this network modulates and controls the release of neurotransmitters within the myocardium.3 There are 4 major GP within epicardial fat pads: (1) the anterior right GP, situated in the fat pad near the base of the right pulmonary veins and adjacent to the caudal end of the sinoatrial node; (2) the inferior right GP, located in the fat pad close to the junction of the inferior vena cava and both atria; (3) the superior left GP, situated in the fat pad between the left superior pulmonary vein–atrial junction and left pulmonary artery; and (4) the inferior left GP, located in the fat pad at the left inferior pulmonary vein–atrial junction.2 Multiple investigations have found that systematic epicardial GP ablation could increase the acute success rate of radiofrequency ablation for AF in patients or canine models,1–6 whereas partial denervation showed controversial results in long-term follow-up.7–10 Therefore, whether systematic epicardial GP ablation could enhance AF ablation in the long term has not been fully clarified.

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In addition, previous investigations have shown that augmented sympathetic tone may increase the vulnerability of ventricular tachyarrhythmias, whereas increased vagal activity has a protective effect on ventricular tachyarrhythmias.11 However, whether atrial denervation can affect ventricular innervation and predispose the heart to ventricular tachyarrhythmias has not been determined.

Therefore, the purposes of the present study were to (1) investigate the long-term electrophysiological outcomes of systematic epicardial GP ablation in the atrium and ventricle in dogs and (2) evaluate the properties of neural remodeling in the atrium and ventricle after systematic epicardial GP ablation.

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Methods

Animal Preparation
All animal studies were reviewed and approved by the Institutional Animal Care and Use Committee at our institution. Twenty-four adult mongrel dogs (18–25 kg) were divided into 3 groups: epicardial GP ablation group 1 (n=8), epicardial GP ablation group 2 (n=8), and a sham operation group (n=8). All dogs were anesthetized with 5% sodium pentobarbital (2–3 mL/kg) given intravenously, followed by an additional dose of 1 mL/kg at the end of each hour. A tracheal cannula was inserted, and intermittent positive pressure ventilation with room air was delivered by a respirator. A 6-lead frontal ECG was recorded continuously during the procedure (filter, 0.05–30 Hz). After left thoracotomy at the fourth intercostal space, the heart was exposed in a pericardial cradle.

GP Ablation
In the 2 epicardial GP ablation groups, the LOM and the fat pads that contain the superior left GP and inferior left GP were exposed by left thoracotomy. After the superior left GP, inferior left GP, and LOM were ablated, the fat pads that contain the anterior right GP and inferior right GP were exposed by lifting up the pericardium, and the anterior right GP and inferior right GP were ablated sequentially through the GP area occupied by the nerves divided by the total area examined (μm²). The nerve density was the area occupied by the nerves in the field. The mean density of nerves in these 3 selected fields was used to represent the nerve density of that section. The immunohistochemical study was done by a pathologist who had no knowledge of our study.

Electrophysiological Study
Before and immediately after ablation, an electrophysiological study was performed on the dogs in epicardial GP ablation group 1 with 4 quadripolar catheters ( Biosense Webster). These catheters were inserted into the right atrium, coronary sinus, His bundle, and right ventricle through the bilateral femoral or jugular veins, or placed in the left ventricle through the femoral artery. The ECG and intracardiac electrograms were amplified and recorded on a computer-based Prucka ComboLab System (General Electric Company, Fairfield City, CT). The same procedure was performed in epicardial GP ablation group 2 and the sham operation group 8 weeks postoperatively.

Immunohistochemical Study
After the electrophysiological study, dogs in epicardial GP ablation group 2 and the sham operation group were euthanized immediately and the hearts were obtained for immunohistochemical study. Tissues were obtained from the left atrial free wall, right atrial free wall, high right atrium, right ventricular free wall, right ventricular outflow tract, left ventricular free wall, and interventricular septum in both groups. These tissues were fixed in neutral buffered formalin for 24 hours and processed into paraffin blocks. The obtained tissues were sectioned at a thickness of 6 μm and stained with tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT) to show sympathetic and parasympathetic nerves, respectively. The tissues were stained in the same session. Nerve densities were determined by a computer-assisted image analysis system ( Image-Pro Plus 3.0; Media Cybernetics, L.P., Silver Spring, MD). Each slide was examined under a microscope to select 3 fields with the highest density of nerves. The computer then calculated the area occupied by the nerves in the field. The nerve density was the area occupied by the nerves divided by the total area examined (μm²). The mean density of nerves in these 3 selected fields was used to represent the nerve density of that section. The immunohistochemical study was done by a pathologist who had no knowledge of our study.

Statistical Analysis
Continuous variables are expressed as medians with first and third quartiles and categorical values are expressed as frequency (%). Measures before and after ablation in the same dogs of epicardial GP ablation group 1 were compared by the Wilcoxon signed-rank test. Any comparisons involving the 3 groups were performed by the Kruskal–Wallis test that simultaneously compares all 3 groups, if the global test comparing the 3 groups is statistically significant, pairwise comparisons were performed using Kruskal–Wallis test with Bonferroni post hoc correction. Categorical variables were analyzed by Fisher exact test. Comparisons that involve multiple locations in each dog were performed by the linear regression analysis for continuous variables or by the logistic regression analysis for categorical variables using generalized estimating equations methods. All analyses were performed with SPSS version 17.0 software (SPSS, Inc, Chicago, IL.). A P value <0.050 was considered statistically significant, and a P value <0.017 was considered statistically significant when Bonferroni post hoc correction was used.

Results

Electrophysiological Study
The end point of GP ablation was achieved in all dogs in the 2 epicardial GP ablation groups after 12 (9; 15) applications of radiofrequency ablation on each GP (Figure 1). The amplitude of atrial electrograms before and after ablation was comparable (10.3 mV [9.2; 12.1] versus 9.9 mV [8.7; 11.6]; P=0.353), indicating that the collateral tissue damage caused by GP ablation was minimal. In epicardial GP ablation group

or S1S2S3 stimulation at all aforementioned sites. During burst pacing, the S1–S3 interval was decreased from 230 ms to refractoriness by decrements of 10 ms. During S1S2S3 stimulation, the S1–S2 and S2–S3 intervals were set at 230 and 180 ms, respectively, and the S2–S3 interval was decreased from 180 ms to refractoriness by decrements of 10 ms. If the induced tachyarrhythmias lasted >10 minutes, low-power (15–30) epicardial cardioversion was performed to minimize the effect of acute myocardial electric remodeling induced by sustained tachycardia. Induction of AF was defined as a rapid (>400 per minute) irregular atrial rhythm lasting for >60 seconds. The tachyarrhythmias’ inducibility was quantified as the number of stimulation or pacing applications that induced tachyarrhythmias, divided by the total number of stimulation or pacing applications. Intracardiac bipolar electrograms were filtered at 30 to 500 Hz. The same procedure was performed in epicardial GP ablation group 2 and the sham operation group 8 weeks postoperatively.
1, the ERP of the atrium was significantly prolonged after ablation (Table 1), whereas the atrial tachyarrhythmias’ inducibility was significantly lower than its preablation level (5.5% versus 15.9%; \( P = 0.019 \)). The ERP of the ventricles was comparable before and after atrial GP ablation (Table 1). No ventricular tachyarrhythmias were induced in this group. Eight weeks after ablation or sham operation, the baseline heart rate in epicardial GP ablation group 2 was higher than that in the sham operation group (166 beats per minute [152; 181] versus 127 beats per minute [109; 135]; \( P = 0.022 \)). The ERP of the high right atrium, low right atrium, coronary sinus proximal, coronary sinus distal, right ventricular apex, right ventricular outflow tract, and left ventricular free wall in epicardial GP ablation group 2 was the shortest among the 3 groups (Figure 2). In epicardial GP ablation group 2, the ERP of the left atrium was shorter than that of the right atrium (70.0 ms [58.0; 81.0] versus 98.5 ms [88.0; 107.0]; \( P = 0.012 \)), whereas the ERP was comparable within the left and right atria. In the sham operation group, the ERPs of the left and right atria were comparable. The ERPs of the left and right ventricles were also comparable in both groups. AF that lasted >10 minutes was induced in 8 dogs in epicardial GP ablation group 2 (Figure 3), whereas just 1 episode of AF that lasted for 200 seconds was induced in 1 dog in the sham operation group. The inducibility of atrial tachyarrhythmias in epicardial GP ablation group 2 was significantly higher than that in the sham operation group (74.9% versus 12.4%; \( P < 0.001 \)). In epicardial GP ablation group 2, the inducibility of atrial tachyarrhythmias in the left atrium (coronary sinus proximal, 94.7%; coronary sinus distal, 90.2%) was higher than that in the right atrium (high right atrium, 53.9%; low right atrium, 61.2%; \( P < 0.001 \)), whereas the inducibility of atrial tachyarrhythmias was comparable within the left or right atrium. In the sham operation group, the inducibility of atrial tachyarrhythmias in the left and right atria was comparable. One dog in epicardial GP ablation group 2 underwent induction of ventricular fibrillation that was refractory to cardioversion. No other dogs in either group underwent induction of ventricular tachyarrhythmias. Notably, the atrial ERP was significantly shorter, and the atrial tachyarrhythmias’ inducibility was significantly higher (74.9% versus 5.5%; \( P < 0.001 \)) in epicardial GP ablation group 2 than in epicardial GP ablation group 1 (Figure 2).

### Autonomic Nerve Density

All TH- and ChAT-immunostained structures had morphologies typical of nerve fibers and were located between myocytes and around blood vessels. The density of TH- and ChAT-positive nerves in the atrium was much higher in epicardial GP ablation group 2 than in the sham operation group, whereas in the ventricle there was no significant difference between the 2 groups in the densities of the 2 types of nerves (Table 2). In epicardial GP ablation group 2, the densities of TH- and ChAT-positive nerves in the left and right atria, as well as those in the left and right ventricles, were comparable. Figures 4 and 5 show typical examples of TH- and ChAT-positive nerve distribution in the hearts of dogs from both groups.

### Discussion

#### Major Findings

To the best of our knowledge, this is the first study to investigate the long-term outcomes of systemic ablation of all 4 epicardial GP and the LOM in both the atrium and the ventricle. This study had 3 major findings. First, systematic epicardial GP ablation not only significantly decreased the ERP of the atrial and ventricular myocardium but also increased the inducibility of atrial tachyarrhythmias at 8-week follow-up. Second, the density of TH- and ChAT-positive nerves in the atrium increased 8 weeks after systematic epicardial GP ablation. Third, systematic epicardial GP ablation did not affect the inducibility of ventricular tachyarrhythmias or the nerve densities in the ventricle.

### Systematic GP Ablation and AF

Recently, numerous studies have been performed to test whether GP ablation can improve the success rate of AF.
ablation, but the results are controversial. Our study found that 8 weeks after GP ablation or sham operation, epicardial GP ablation group 2 had the shortest atrial and ventricular ERP and the highest inducibility of atrial tachyarrhythmias compared with epicardial GP ablation group 1 and the sham operation group. These findings have several possible explanations. (1) In this study, we did not isolate pulmonary veins, which may explain the difference between our findings and those of clinical studies in which GP ablation seemed to have a better outcome. (2) The atrial denervation was incomplete. Although we completely ablated all 4 visible major GP and the LOM, it is known that there is an average of 619 GP distributed throughout the canine heart. A previous study showed that although a majority of nerve bundles are located within the epicardial fat pad, up to one third of the nerve bundles of the atrium are located in the adjoining/sublying myocardium, away from the fatty tissue. Furthermore, there are efferent nerve fibers that bypass the different GP in dogs. Therefore, total denervation of the canine heart is hardly achievable with the techniques currently available. (3) The atrial natriuretic peptide level of the atrium was increased. A previous study found that 8 weeks after GP ablation, the levels of atrial natriuretic peptide increased significantly, which may decrease the atrial conduction time and ERP by decreasing the transient outward K+ current in atrial cells and increasing the vagal tone, thereby providing a potential electrophysiological

Figure 2. The effective refractory period in dogs of the epicardial ganglion plexi (GP) ablation group 1, the epicardial GP ablation group 2, and the sham operation group. Data are expressed as medians with first and third quartiles. CSd indicates coronary sinus distal; CSp, coronary sinus proximal; ERP, effective refractory period; HRA, high right atrium; LRA, low right atrium; LVFW, left ventricular free wall; RVA, right ventricular apex; and RVOT, right ventricular outflow tract.

Figure 3. Atrial fibrillation (AF) induced by programmed stimulation. After a train of S1S2 pacing (S1-S2 interval was 260 ms), a premature extrastimulus (arrow) caused a period of sustained AF when the S1-S2 interval was 90 ms.
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substrate for arrhythmias. The end-organ sensitivity was increased. It has been found that an increased density of muscarinic receptors and β-receptors, owing to the decreased level of neural transmitters, promoted AF in a canine denervation model and in a heart failure model. Hyper-reinnervation of the neural network occurred. Through immunohistochemical study, the present study found atrial parasympathetic and sympathetic hyper-reinnervation 8 weeks after GP ablation. The atrial hyper-reinnervation after GP ablation could be explained by the following mechanisms: First, because we could not achieve complete denervation by ablating the principal GP and the LOM, there are still cardiac neural elements spread over the atrium, and they can reinnervate the atrium by axonal regeneration. Second, applying radiofrequency energy to GP may destroy bypassing neural axons, which may regenerate after the damage. Third, radiofrequency energy increases the expression of nerve growth factor by long-term synaptic potentiation and kindling stimulations. Either nerve injury or radiofrequency energy stimulation can result in increased local nerve growth factor production. These nerve growth factors can be transported to remaining GP or stellate ganglia through axonal retrograde transport. Increased nerve-sprouting activity within the remaining GP and stellate ganglion can cause extensive cardiac nerve sprouting. Fourth, it is possible that intense and repetitive HFS of the GP may have induced the observed hyper-innervation, even at distant sites. Thus, one possible explanation of the results of our study is that because GP ablation leads to atrial hyper-reinnervation involving both sympathetic and parasympathetic nerves by the mechanisms mentioned above, the increased parasympathetic neurotransmitters could further decrease atrial ERP. Meanwhile, the increased sympathetic neurotransmitters could further increase the incidence of early afterdepolarizations. Theoretically, both the atrial ERP shortening and early afterdepolarization of the atrial myocytes could increase the heart’s vulnerability to atrial tachyarrhythmias.

Effect of GP Ablation on the Ventricle

Our study found that the inducibility of ventricular tachyarrhythmias among the 3 groups was comparable and there were differences in the nerve densities of different cardiac regions. The nerve densities of TH-positive and ChAT-positive nerves in the GP ablation group and sham operation group are shown in Table 2.

Table 2. Nerve Densities (μm²/mm²)

<table>
<thead>
<tr>
<th>Location</th>
<th>TH-Positive Nerve Densities</th>
<th>ChAT-Positive Nerve Densities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epicardial GP</td>
<td>Sham Operation Group</td>
</tr>
<tr>
<td></td>
<td>Ablation Group 2</td>
<td></td>
</tr>
<tr>
<td>LAFW</td>
<td>1468.0 (1012.5; 1625.5)</td>
<td>235.5 (120.8; 320.0)</td>
</tr>
<tr>
<td>RAFW</td>
<td>1244.5 (715.0; 1530.8)</td>
<td>269.0 (179.8; 375.0)</td>
</tr>
<tr>
<td>HRA</td>
<td>1050.5 (576.8; 1256.8)</td>
<td>180.0 (105.0; 237.8)</td>
</tr>
<tr>
<td>RFW</td>
<td>486.5 (468.8; 516.8)</td>
<td>245.0 (164.5; 355.0)</td>
</tr>
<tr>
<td>RVOT</td>
<td>597.5 (314.0; 749.0)</td>
<td>559.0 (154.3; 686.8)</td>
</tr>
<tr>
<td>LVFW</td>
<td>253.0 (81.0; 390.0)</td>
<td>282.0 (201.0; 411.3)</td>
</tr>
<tr>
<td>RVOT</td>
<td>333.5 (183.5; 501.8)</td>
<td>524.5 (406.8; 546.8)</td>
</tr>
<tr>
<td>LVFW</td>
<td>1875.0 (1352.0; 1979.5)</td>
<td>354.5 (270.5; 423.5)</td>
</tr>
<tr>
<td>RAFW</td>
<td>1481.0 (1055.8; 1612.8)</td>
<td>232.0 (70.3; 442.3)</td>
</tr>
<tr>
<td>HRA</td>
<td>935.5 (798.5; 986.5)</td>
<td>99.5 (42.3; 195.0)</td>
</tr>
<tr>
<td>RFW</td>
<td>160.0 (61.5; 201.0)</td>
<td>76.0 (63.8; 137.5)</td>
</tr>
<tr>
<td>RVOT</td>
<td>223.0 (207.5; 236.0)</td>
<td>171.5 (128.3; 197.8)</td>
</tr>
<tr>
<td>LVFW</td>
<td>65.5 (36.8; 101.8)</td>
<td>123.0 (94.0; 135.0)</td>
</tr>
<tr>
<td>RVOT</td>
<td>98.0 (70.0; 128.5)</td>
<td>116.0 (97.0; 135.3)</td>
</tr>
</tbody>
</table>

Data are expressed as medians with first and third quartiles. ChAT indicates choline acetyltransferase; GP, ganglionated plexi; HRA, high right atrium; IVS, interventricular septum; LAFW, left atrial free wall; LVFW, left ventricular free wall; RAfw, right atrial free wall; RVFW, right ventricular free wall; RVOT, right ventricular outflow tract; and TH, tyrosine hydroxylase.

Figure 4. Examples of immunohistochemical staining of choline acetyltransferase–positive nerves (arrow). A, Left atrium free wall 8 wk after ganglionated plexi (GP) ablation. B, Left atrium free wall 8 wk after sham operation. C, Right ventricular outflow tract 8 wk after GP ablation. D, Right ventricular outflow tract 8 wk after sham operation (magnification ×40).
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no significant intergroup differences in the densities of TH- and ChAT-positive nerves within the ventricle. These results show that this denervation procedure did not affect ventricular innervation and should not decrease the potential protective effects of vagal tone on the ventricle. However, our study found that the ERP of the ventricular myocardium in epicardial GP ablation group 2 was significantly shorter than that in the sham operation group. The ERP shortening might be the mechanism responsible for the ventricular fibrillation induced in 1 dog in epicardial GP ablation group 2. Although the ventricular ERP shortening has few clinical implications in the structurally normal heart, it may be proarrhythmic in hearts with structural disease, such as myocardial infarction or heart failure.

Limitations
There are several limitations to our study. First, although epicardial HFS-guided GP ablation enables the operator to judge whether a given GP has been destroyed while minimizing collateral atrial injury, this approach may not destroy as many GP as anatomy-based GP ablation, as indicated in a recent work by Pokushalov et al.\textsuperscript{5} Second, we did not measure nerve growth factor mRNA or protein in addition to atrial natriuretic peptide, so we did not elucidate the relationship between these biological molecules and neural remodeling. Third, the follow-up period in this study was only 8 weeks. We could not determine whether the regenerated nerves can be preserved over a longer period because we did not determine whether these nerves formed functional synapses with the myocardium, which is necessary for regenerated nerves to exist. Fourth, atrial innervation is similar between human beings and dogs in terms of location; in particular, both species have 4 major atrial GP. However, human beings have a larger number of total GP than dogs have. Therefore, caution should be used in extrapolating our findings to clinical situations.

Conclusions
After 8 weeks of healing, epicardial GP ablation without additional atrial ablation is potentially proarrhythmic, which may be attributable to decreased atrial ERP and atrial hyperreinnervation involving both sympathetic and parasympathetic nerves. At the ventricular level, this procedure decreased the ventricular ERP but had no effect on the inducibility of ventricular tachyarrhythmias or on ventricular innervation.

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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

Surgical, as well as catheter-based ablation of the retroatrial ganglionated plexi, has been pursued as a technique to improve success rates with ablation for atrial fibrillation. However, the long-term effects of standalone ganglia ablation have not been established. The present canine study showed that after 8 weeks, regional ganglionated plexi ablation without pulmonary vein isolation is potentially proarrhythmic with decreased atrial effective refractory period and evidence for sympathetic and parasympathetic atrial hyper-reinnervation. Further study is needed to establish whether additional pulmonary vein isolation or more global cardiac denervation may offset these possibly proarrhythmic effects and result in improved clinical outcomes.
Ablation of Epicardial Ganglionated Plexi Increases Atrial Vulnerability to Arrhythmias in Dogs
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