Atrial Fibrillation Begets Atrial Fibrillation

Autonomic Mechanism for Atrial Electrical Remodeling Induced by Short-Term Rapid Atrial Pacing

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Background—The mechanism(s) for acute changes in electrophysiological properties of the atria during rapid pacing induced atrial fibrillation (AF) is not completely understood. We sought to evaluate the contribution of the intrinsic cardiac autonomic nervous system in acute atrial electrical remodeling and AF induced by 6-hour rapid atrial pacing.

Methods and Results—Continuous rapid pacing (1200 bpm, 2× threshold [TH]) was performed at the left atrial appendage. Group 1 (n=7) underwent 6-hour pacing immediately followed by ganglionated plexi (GP) ablation; group 2 (n=7) underwent GP ablation immediately followed by 6-hour pacing; and group 3 (n=4) underwent administration of autonomic blockers, atropine (1 mg/kg), and propranolol (0.6 mg/kg) immediately followed by 6-hour pacing. The effective refractory period (ERP) and window of vulnerability (WOV, in milliseconds), ie, the difference between the longest and the shortest coupling interval of the premature stimulus that induced AF, were measured at 2×TH and 10×TH at the left atrium, right atrium, and pulmonary veins every hour before and after GP ablation or autonomic blockade. In group 1, ERP was markedly shortened in the first 2 hours and then stabilized both at 2×TH and 10×TH; however, WOV was progressively widened throughout the 6-hour period. After GP ablation, ERP was significantly longer than before ablation and AF could not be induced (WOV=0) at either 2×TH or 10×TH. In groups 2 and 3, rapid atrial pacing failed to shorten the ERP. AF could not be induced in 6 of 7 dogs in group 2 and all 4 dogs in group 3 during the 6-hour pacing period.

Conclusion—The intrinsic cardiac autonomic nervous system plays a crucial role in the acute stages of atrial electrical remodeling induced by rapid atrial pacing. (Circ Arrhythmia Electrophysiol. 2008;1:184-192.)

Key Words: atrial fibrillation • remodeling • autonomic nerve system

In 1995, Wijffels and coworkers1 found that continuous rapid atrial pacing in the goat heart leads to progressive shortening of the atrial effective refractory period (ERP) and increased duration of atrial fibrillation (AF) once it is induced. The longer the duration of atrial pacing, the longer the AF was maintained. This phenomenon, called as “AF begets AF,” has attracted clinical attention because it accounts for the clinical observation that recurrent episodes of paroxysmal AF often progresses to more persistent forms of AF. In the past decade, tachycardia-induced atrial remodeling was found to be associated with alterations in expression of ion channels and changes in the structure of the atria.2,3 Recently, several studies4–11 from our institute demonstrated that the intrinsic cardiac autonomic nervous system (ICANS) plays an important role in the initiation and maintenance of AF. We hypothesized that the ICANS may be another remodeling mechanism leading to the phenomenon of “AF begets AF.” Using a 6-hour rapid atrial pacing model modified from Wijffels et al.1 we examined the effect of the ICANS on the acute atrial remodeling process by the ablation of the ganglionated plexi (GP) located in atrial epicardial fat pads and by the administration of autonomic blockers.

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Methods

Animal Preparation
All animal studies were reviewed and approved by the institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center. Eighteen adult mongrel dogs weighing 20 to 25 kg were anesthetized with 50 mg/kg Na-pentobarbital and ventilated with room air with a positive pressure respirator. Core body

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Pacing was temporarily stopped to measure the ERP and AF inducibility. Programmed stimulation at atrial myocardial sites or PV sleeves was performed using a Medtronic programmable stimulator (model 5328; Medtronic Inc, Minneapolis, MI). The ERP at an atrial pacing cycle length of 330 ms, was determined at both 2× diastolic threshold and 10× diastolic threshold (TH=0.1 to 1.0 mA). The S1-S2 intervals were decreased from 150 ms to refractoriness initially by decrements of 10 ms (S1:S2=8:1). As the S1-S2 intervals approached the ERP, decrements were reduced to 1 ms. ERP dispersion was defined as the coefficient of variation (standard deviation/mean) of the ERP at all 7 sites (LSPV, LPV, LA, RSPV, RIPV, RA, and RAA).12

We used the window of vulnerability (WOV) as a quantitative measure of AF inducibility.2 AF was defined as irregular atrial rates faster than 500 bpm associated with irregular atrioventricular conduction lasting >5 seconds (Supplementary Figure 1). During ERP measurements, if AF was induced by decremental S1S2 stimulation, the longest and the shortest S1-S2 interval (in ms) at which AF was induced were then determined.9 The difference between the two was designated as the WOV.2 The ΣWOV was counted as the sum of WOV acquired at 2×TH and 10×TH at all sites in each dog. The time for determining the ERP and WOV after each hour of pacing was less than 15 minutes in most cases (13.9±5.0 minutes).

**GP Ablation**

The anterior right ganglionated plexi (ARGP) located in the fat pad at the RSPV-atrial junction was localized by applying high frequency stimulation (HFS; 20Hz, 0.1ms duration, 0.6 to 4.5 V) with a bipolar stimulation-ablation probe electrode (AtriCure, West Chester, OH).9–11 In this voltage range, progressive slowing of the sinus rate was observed directly related to the voltage applied. The same device was later used to deliver radiofrequency current to ablate the ARGP.9–11 The inferior right ganglionated plexi (IRGP) located at the junction of inferior vena cava and both atria, the superior left ganglionated plexi (SLGP) at the LSPV-atrial junction, the inferior left ganglionated plexi (ILGP) adjacent to the LIPV, and autonomic neural elements along the ligament of Marshall (LOM) were also localized by the effect of HFS, which either slowed the sinus rate or suppressed the AV conduction. These areas were subsequently ablated using the same device. Complete ablation of each GP or LOM was verified by applying maximal strength of stimulation (12V) that failed to slow the sinus rate or inhibit the AV conduction. The ablation was limited to GP/fat pad, and the morphology and amplitude of the electrograms at the sites closest to the fat pad were not altered after ablation, indicating that the collateral tissue damage caused by GP ablation was minimal. The time for locating and ablating the GP/fat pad was less than 15 minutes in each dog.

**Administration of Autonomic Blockers**

Both parasympathetic and sympathetic systems were blocked by administration of autonomic blockers, atropine and propranolol, in 4 dogs before 6-hour atrial pacing. Atropine and propranolol were administered according to the previous report by Wijffels et al.13 Atropine sulfate (Sigma-Aldrich Inc, St. Louis, MO) was infused intravenously in cumulative doses of 0.1, 0.3, 0.6, and 1.0 mg/kg in steps of 10 minutes. Propranolol HCl (Sigma-Aldrich Inc, St. Louis, MO) was given in a similar way in cumulative dosages of 0.1, 0.3, and 0.6 mg/kg.

**Experiment Protocol**

Eighteen dogs were assigned into 3 groups: group 1 (n=7): 6-hour atrial pacing immediately followed by GP (ARGP+IRGP+SLGP+ILGP+LOM) ablation; Group 2 (n=7): GP (ARGP+IRGP+SLGP+ILGP+LOM) ablation immediately followed by atrial pacing for 6 hours; Group 3 (n=4): Administration of autonomic blockers immediately followed by 6-hour atrial pacing. The ERP and WOV were measured at LSPV, LPV, LA, RSPV, RIPV, RA, and RAA every hour during the 6-hours pacing period before and after GP ablation or autonomic blockade.

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**Figure 1.** Schematic representation and catheter position in the atria. A. Left thoracotomy approach. SLGP is located adjacent to the junction of LSPV and LA, and ILGP is located near the junction of LIPV and LA. Multielectrode catheters were sutured to the LSPV, LPV, LA, and left atrial appendage (LAA). Continuous rapid pacing (1200 bpm) was performed at the LAA. LV indicates left ventricle; RV, right ventricle. B. Right thoracotomy approach. ARGP is located adjacent to the RSPV near the atrial junction, and IRGP is located at the junction of the inferior vena cava (IVC) and both atria. Similarly, multielectrode catheters were sutured to RSPV, RIPV, RA, and RAA. SVC indicates superior vena cava. SLGP indicates superior left ganglionated plexi; LSPV, left superior pulmonary vein; LA, left atrium; ILGP, inferior left ganglionated plexi; LPV, left inferior pulmonary vein; ARGP, anterior right ganglionated plexi; RSPV, right superior pulmonary vein; IRGP, inferior right ganglionated plexi; IVC, inferior vena cava; RIPV, right inferior pulmonary vein; RA, right atrium; RAA, right atrial appendage; LPA, left pulmonary artery; LOM, ligament of Marshall.

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Temperature was maintained at 36.5±1.5°C. Standard ECG leads were continuously recorded to determine the heart rate and rhythm. Blood pressure (BP) was continuously monitored via a pressure transducer positioned in the right femoral artery.

The chest was entered via a left thoracotomy at the fourth intercostal space. Multielectrode catheters were sutured to the LSPV, LPV, LA, and left atrial appendage (LAA). Continuous rapid pacing (1200 bpm) was performed at the LAA. LV indicates left ventricle; RV, right ventricle.

**Programmed Stimulation**

Rapid atrial pacing was delivered (1200 bpm, 2× threshold, 1 ms in duration) at the left atrial appendage. After each pacing hour, rapid atrial
Histological Studies
The fat pads containing ARGP from animals after ablation (4 dogs) and without ablation (1 dog) were removed and fixed in neutral buffered formalin for 24 hours and processed into paraffin blocks. Cross sections of the ablated area were sectioned at 6 µm thickness and stained with hematoxylin and eosin. Digital photographs were taken. The panoramic view was produced by reconstruction of multiple images of the same piece of specimen by Adobe Photoshop 7.0.

Statistical Analysis
All values were expressed as mean ± standard deviation. Paired t test was used for comparisons of ERP and WOV before and after GP ablation. ANOVA for repeated measurements was used for comparisons of the ERP or WOV among different pacing hours and followed by post hoc testing (least significant differences) for comparisons of the ERP and WOV at the end of each subsequent hour of pacing versus ERP and WOV in the baseline state. Statistical significance was defined as P≤0.05.

Results
The systolic and diastolic blood pressures were stable during the entire period of experiments, and no evident sign of heart failure was observed throughout the 6-hours pacing period.

ERP and WOV
In group 1 (GP ablation after 6-hour pacing, Figure 2), ERP was markedly shortened in the first 2 hours, but longer periods of rapid pacing (3 to 6 hours) failed to further shorten the ERP at either 2×TH or 10×TH at each site (Figure 2A to 2G, ERP). In contrast, ΣWOV was progressively widened throughout the 6-hour pacing period (Figure 2H). For instance, the ERP at LSPV was shortened from 125±19 ms in the baseline state to 96±14 ms at the end of 2 hours of pacing (2×TH; P<0.05). The ERP was stabilized at 90 to 100 ms from the third to the sixth pacing hours. The WOV at LSPV progressively increased from 5 ms in the baseline state to 319 ms at the end of the 6-hours
pacing period (not shown in Figure 2). After GP (ARGP+IRGP+SLGP+ILGP+LOM) ablation, ERP was lengthened to the baseline level and AF could no longer be induced (WOV=0) at all pacing sites at either 2×TH or 10×TH (Figure 2, after GP ablation).

In group 2 (GP ablation before 6-hour pacing, Figure 3), rapid atrial pacing failed to shorten the ERP at any site (Figure 3A to 3G). AF could not be induced (WOV=0) in 6 of 7 dogs during the 6-hour pacing and was inducible in 1 of 7 with WOV of only 10 ms at 10×TH. SLGP indicates superior left ganglionated plexi; LSPV, left superior pulmonary vein; LA, left atrium; ILGP, inferior left ganglionated plexi; LIPV, left inferior pulmonary vein; ARGP, anterior right ganglionated plexi; RIPV, right inferior ganglionated plexi; RA, right atrium; RAA, right atrial appendage; LOM, ligament of Marshall; ERP, effective refractory period; WOV, window of vulnerability; GP, ganglionated plexi; AF, atrial fibrillation; Abl, ablation; TH, threshold.

### ERP Dispersion

In group 1, the ERP dispersion was increased at the first hour and then stabilized during the second to sixth hour after pacing was started. The increase in ERP dispersion induced by 6-hour pacing was eliminated by GP ablation (Table 1). However, these changes did not achieve statistical significance (ANOVA; end of the sixth pacing hour versus immediately after GP ablation; 2×TH: P=0.08; 10×TH: P=0.10).

In group 2, after GP were ablated, 6-hour pacing failed to increase the ERP dispersion at all (Table 2).

### Histological Studies

Figure 5 illustrates an example of the histological studies of the fat pad containing ARGP after ablation or without ablation. After GP ablation, the autonomic ganglia were
destroyed and the damage to the surrounding myocardial tissue was minimal.

**Discussion**

**Main Findings**

In this acute study of AF facilitated by rapid atrial pacing, the ERP was markedly shortened in the first 2 hours and the WOV was progressively widened throughout the 6-hour pacing period (Figure 2). Ablation of the 4 main GP and LOM in the atria reversed the effects of ERP shortening and also eliminated AF inducibility at all sites. Moreover, in the animals receiving GP ablation or autonomic blockade first, rapid atrial pacing failed to shorten the ERP and AF could not be induced with programmed stimulation in 6 of 7 dogs (group 2) and all 4 dogs (group 3) during the 6-hour pacing period. These results strongly suggest that the ICANS, specifically the GP, plays a critical role in acute atrial electrical remodeling induced by rapid atrial pacing.

**Table 1. Effective Refractory Period (ERP) Dispersion During 6-Hour Pacing and After Ganglionated Plexi (GP) Ablation in Group 1 (n=7)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1st-Hour Pacing</th>
<th>2nd-Hour Pacing</th>
<th>3rd-Hour Pacing</th>
<th>4th-Hour Pacing</th>
<th>5th-Hour Pacing</th>
<th>6th-Hour Pacing</th>
<th>GP Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2×TH</td>
<td>0.08±0.05</td>
<td>0.11±0.04</td>
<td>0.11±0.05</td>
<td>0.1±0.03</td>
<td>0.12±0.05</td>
<td>0.11±0.06</td>
<td>0.13±0.05</td>
<td>0.06±0.02</td>
</tr>
<tr>
<td>10×TH</td>
<td>0.17±0.06</td>
<td>0.26±0.09</td>
<td>0.21±0.06</td>
<td>0.23±0.15</td>
<td>0.22±0.1</td>
<td>0.19±0.07</td>
<td>0.23±0.05</td>
<td>0.13±0.04</td>
</tr>
</tbody>
</table>

ERP dispersion was taken as the coefficient of variation (standard deviation/mean) of the ERP at all seven sites (left superior pulmonary vein, left inferior pulmonary vein, left atrium, right superior pulmonary vein, right inferior pulmonary vein, right atrium, and right atrial appendage). TH indicates threshold.
Mechanisms Underlying “AF begets AF”

The mechanism underlying AF was considered to be multiple wavelet reentry since Moe et al. proposed that hypothesis. However, recent studies showed that rapid focal discharges particularly from the PVs are the initiators of AF in many patients with paroxysmal or persistent AF. In an animal model of rapid atrial pacing, Morillo et al. reported that an area in the posterior LA near the PV-LA junction uniformly had the shortest AF cycle length, which was presumably a focal driver for maintenance of AF. In another group of studies using a computerized high-density electrode mapping array, Zhou et al. and Chou et al. demonstrated intermittent focal discharges at the PVs, which cannot be suppressed by ibutilide (a class III antiarrhythmic drug), in a canine model of AF induced by chronic rapid atrial pacing. These observations raised the possibility that both multiwave reentry and rapid focal discharges may be the mechanisms operative in the phenomenon of “AF begets AF.”

Recent studies from our laboratory have shown that focal AF can be induced or eliminated by stimulating or interrupting the ICANS. Within the ICANS, the GP contain the greatest number of neural elements, both parasympathetic and sympathetic. Along with the results presented in this study, we hypothesize that GP ablation diminishes the trigger activities and prevents the shortening of ERP across the atrium, leading to more homogenous distribution of ERP, which prevents multiwave reentry. In other words, GP ablation may diminish or eliminate AF resulting from both rapid focal discharges and multiwave reentry.

Mechanisms Underlying Atrial Electric Remodeling Induced by Acute Rapid Atrial Pacing (≤6 hours)

Both structural remodeling and electrical remodeling have been demonstrated to facilitate the initiation and maintenance of AF in the atrial pacing model. Tachycardia-induced structural remodeling cannot explain the results presented in this study because the structural changes of atria would require at least several days of pacing. Atrial electrical remodeling is thought to result mainly from Ca2+ overload induced by frequent depolarizations (rapid pacing), leading to alterations of ion channels, especially decreased ICa,L, which subsequently shorten the atrial action potential duration and refractoriness. However, electrical remodeling of the

Table 2. Effective Refractory Period (ERP) Dispersion After Ganglionated Plexi (GP) Ablation Followed by 6-Hour Atrial Pacing in Group 2 (n=7)

<table>
<thead>
<tr>
<th></th>
<th>GP Ablation</th>
<th>1st-Hour Pacing</th>
<th>2nd-Hour Pacing</th>
<th>3rd-Hour Pacing</th>
<th>4th-Hour Pacing</th>
<th>5th-Hour Pacing</th>
<th>6th-Hour Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2×TH</td>
<td>0.11±0.05</td>
<td>0.12±0.05</td>
<td>0.12±0.04</td>
<td>0.12±0.04</td>
<td>0.11±0.03</td>
<td>0.11±0.04</td>
<td>0.11±0.02</td>
</tr>
<tr>
<td>10×TH</td>
<td>0.13±0.02</td>
<td>0.15±0.03</td>
<td>0.14±0.03</td>
<td>0.12±0.02</td>
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<td>0.11±0.03</td>
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</table>

ERP dispersion was taken as the coefficient of variation (standard deviation/mean) of the ERP at all seven sites (left superior pulmonary vein, left inferior pulmonary vein, left atrium, right superior pulmonary vein, right inferior pulmonary vein, right atrium, and right atrial appendage). TH indicates threshold.
atria cannot be explained solely by Ca\(^{2+}\) overload and a decrease of I\(_{\text{Ca,L}}\) induced by frequent depolarizations as it was prevented by interruption of the ICANS (group 2 and group 3) before the initiation of atrial pacing in the present study. It has been proposed that increased ERP dispersion plays a vital role in the chronic atrial pacing model.\(^{12}\) In the present study, we observed a trend of increase in the ERP dispersion, which was eliminated by GP ablation in group 1 (Table 1). The differences did not reach statistical significance, possibly because of a relatively short duration of pacing (6 hours) and a small sample size (n=7). In group 2 animals, the GP were ablated first, this trend in ERP dispersion increase, as observed in group 1 animals, was not observed (Table 2). These findings imply that the antifibrillatory effect of GP ablation may result, in part, from reducing the ERP dispersion.

In the study of Wijffels et al.,\(^{1}\) they postulated that the changes in activity or sensitivity of the ICANS may be one of the mechanisms underlying the electrical remodeling induced by rapid atrial pacing. They later\(^{13}\) found that administration of autonomic blockers, atropine and propranolol, partially reverse the pacing-induced shortening of ERP. Of note, atropine or propranolol was administrated after AF had sustained for 1 to 3 days after chronic atrial pacing. The discrepancy between the results of that study (chronic pacing) and the present study (acute pacing) suggests that different mechanisms may underlie the atrial remodeling induced by short-term and long-term pacing. Alterations of ion channel expression and changes in atrial structure play a predominant role in atrial remodeling induced by longer periods of pacing, whereas changes in the ICANS may be an important factor in atrial remodeling induced by short-term rapid pacing.

The present study indicated that ICANS is strongly associated with acute atrial remodeling induced by rapid atrial pacing. As shown in group 2 and group 3, with the blockade of ICANS by GP ablation or administration of autonomic blockers, atrial electrical remodeling (shortening of ERP and increasing vulnerability of AF) was prevented. We hypothesize that ERP shortening is due in part to the local release of autonomic neurotransmitters, particularly acetylcholine, at the nerve endings that are distributed heterogeneously within the atria and PVs. Therefore, GP ablation and autonomic blockade would not only prolong ERP but also resist the effect of autonomic neurotransmitters in response to rapid atrial pacing. Several possible mechanisms may be responsible for the observation that AF was prevented by blockade of ICANS: (1) A large portion of the atria was protected by the significantly prolonged ERP induced by blockade of ICANS; in other words, multiple wavelets may not be able to propagate to a large portion of the atria, leading to a significant reduction of the functional critical mass for AF to sustain. (2) The innervation and activity of the ICANS may be increased by rapid atrial pacing as shown by Jayachandran et al\(^{12}\) that rapid atrial pacing induced a heterogeneous increase in innervation and activity of atrial sympathetic nervous system, termed as “autonomic remodeling,” which potentially can facilitate the development of AF. In the present study, GP ablation caused uniformity of ERP at several sites. This effect, in turn, would decrease dispersion of refractoriness creating less favorable conduction for AF inducibility. (3) Ion channels modulated by autonomic tone, such as I\(_{\text{K,ACH}}\) (a constitutively active component of I\(_{\text{K,ACh}}\)), which plays a role in atrial electrical remodeling, may be inhibited by the interruption of the ICANS.\(^{22-24}\)

**Clinical Implications**

GP have been shown to be the “integration centers” to modulate electrophysiological functions of the ICANS.\(^9,10\) Inhibition of the ICANS prevents atrial electrical remodeling induced by short-term rapid atrial pacing. The ICANS may play an important role in the progression of
paroxysmal AF lasting from several minutes to several hours, to persistent AF lasting several days. This progression may be prevented by interruption of the ICANS, specifically ablation of the GP. Moreover, in persistent AF patients with mildly to moderately remodeled atria, GP ablation might reverse the remodeling process and impede or reverse the progression of AF.

Study Limitations
First, the present study strongly suggests that ICANS is associated in the acute electrical remodeling induced by rapid atrial pacing; however, we did not have recordings of neural activity to provide direct evidence for the involvement of autonomic activation in these pathophysiological processes. Further study will be needed to provide neurophysiologic evidence of the involvement of the ICANS. Second, in group 1, reverse remodeling might have occurred during the period when localization and ablation of the GP, leading to lengthening of the ERP and shortening of the WOV. A set of control experiments were then performed. After 6-hour pacing, GP were not ablated. Instead, the mean ERP and cumulative WOV were measured 30 and 60 minutes after termination of pacing. The mean ERP and cumulative WOV did not significantly change within 1 hour after the pacing was discontinued (Figure 6). This observation indicates that, compared with GP ablation, the reverse remodeling occurred during localizing and ablating the GP (<15 minutes) was a minor factor contributing to the change of ERP and WOV after GP ablation. Thirdly, the large numbers of tests were performed in small sample sizes (n = 7), which might have affected the statistical power to detect differences of ERP and ERP dispersion among 6 pacing hours. Finally, the long-term effects of autonomic denervation will acquire the statistical power to detect differences of ERP performed in small sample sizes (n = 7), which might have affected the statistical power to detect differences of ERP and ERP dispersion among 6 pacing hours. Finally, the long-term effects of autonomic denervation will acquire future studies to elucidate the role of the ICANS in chronic atrial pacing models.

Conclusions
We conclude that blockade of the ICANS before or after 6-hour pacing prevents or reverses the process of atrial electrical remodeling induced by short-term atrial pacing. Some of the mechanisms operative in the atrial electrical remodeling induced by rapid pacing in the normal dogs may be altered by the effects of interruption of the ICANS. The actions or hyperactivity of the ICANS itself may be a crucial element in acute atrial remodeling. These findings suggest that the ICANS is crucial for the process of “AF begets AF,” at least, in the acute phase.

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Disclosures
None.

References


CLINICAL PERSPECTIVE

The mechanism(s) for acute changes in electrophysiological properties of the atria during rapid pacing induced atrial fibrillation (AF) is not completely understood. This canine study showed that interruption of the intrinsic cardiac autonomic nervous system (ICANS) by ablation of the ganglionated plexi or administration of autonomic blockers, reversed or prevented the electrical remodeling induced by 6-hour rapid atrial pacing, indicating that the ICANS plays a crucial role in the acute stages of atrial electric remodeling induced by rapid atrial pacing. The ICANS may play an important role in the progression of paroxysmal AF lasting from several minutes to several hours, to persistent AF lasting several days. This progression may be prevented by interruption of the ICANS, specifically ablation of the ganglionated plexi. Moreover, in persistent AF patients with mildly to moderately remodeled atria, ganglionated plexi ablation might reverse the remodeling process and impede or reverse the progression of AF.
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