Pulmonary Vein Region Ablation in Experimental Vagal Atrial Fibrillation
Role of Pulmonary Veins Versus Autonomic Ganglia

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Background—Pulmonary vein (PV) –encircling radiofrequency ablation frequently is effective in vagal atrial fibrillation (AF), and there is evidence that PVs may be particularly prone to cholinergically induced arrhythmia mechanisms. However, PV ablation procedures also can affect intracardiac autonomic ganglia. The present study examined the relative role of PVs versus peri-PV autonomic ganglia in an experimental vagal AF model.

Methods and Results—Cholinergic AF was studied under carbachol infusion in coronary perfused canine left atrial PV preparations in vitro and with cervical vagal stimulation in vivo. Carbachol caused dose-dependent AF promotion in vitro, which was not affected by excision of all PVs. Sustained AF could be induced easily in all dogs during vagal nerve stimulation in vivo both before and after isolation of all PVs with encircling lesions created by a bipolar radiofrequency ablation clamp device. PV elimination had no effect on atrial effective refractory period or its responses to cholinergic stimulation. Autonomic ganglia were identified by bradycardic and/or tachycardic responses to high-frequency subthreshold local stimulation. Ablation of the autonomic ganglia overlying all PV ostia suppressed the effective refractory period–abbreviating and AF-promoting effects of cervical vagal stimulation, whereas ablation of only left- or right-sided PV ostial ganglia failed to suppress AF. Dominant-frequency analysis suggested that the success of ablation in suppressing vagal AF depended on the elimination of high-frequency driver regions.

Conclusions—Intact PVs are not needed for maintenance of experimental cholinergic AF. Ablation of the autonomic ganglia at the base of the PVs suppresses vagal responses and may contribute to the effectiveness of PV-directed ablation procedures in vagal AF. (Circulation. 2008;117:470-477.)

Key Words: ablation • fibrillation • model, animal • pulmonary veins

Ablation procedures targeting the pulmonary vein (PV) region are becoming increasingly important in the treatment of atrial fibrillation (AF).1 The autonomic nervous system plays a significant role in AF,2 with vagal influences being particularly effective in promoting AF maintenance.3,4 PV-targeting procedures can prevent the recurrence of vagotonic AF,5 and vagal denervation may contribute to the efficacy of PV-directed AF ablation.6

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The PVs may be a susceptible site for vagally induced arrhythmogenesis. Acetylcholine induces tachycardias resulting from preferential PV reentry, implicating vagally induced PV tachycardias as a potential mechanism in paroxysmal AF.7 Electric or acetylcholine-induced stimulation of cardiac autonomic ganglia induces focal PV firing, which leads to AF in dogs.8,9 Autonomic nerve stimulation reduces PV-sleeve action potential duration and causes triggered PV firing that is suppressed by muscarinic cholinergic receptor blockade, β-adrenoceptor antagonism, inhibition of Ca2+ transients, or Na+-Ca2+ exchange blockade.10 Fibrillatory cycle length shortening in response to vagal stimulation points to vagal effects on PV drivers.11 Thus, eliminating the PVs could suppress vagal AF by removing the vagally enhanced PV drivers that maintain the arrhythmia.

There also is evidence that PV-directed ablation procedures interfere with autonomic innervation. Atrial autonomic nerve density is highest in the region of the PVs.12 Vagal denervation is common after circumferential left atrial (LA) ablation, correlating with reduced AF recurrence.12 Ablation

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of lesions targeting sites (often at the PVs) with vagal reflexes elicited by high-frequency transcatheater stimulation prevents AF recurrence in some patients with vagal AF.11 Thus, PV ablation procedures also could suppress vagal AF by interfering with vagal innervation.

Two potential mechanisms may therefore explain PV involvement in vagal AF: a primary role as preferential targets of vagally induced arrhythmogenesis and driver function and localization close to key autonomic nervous structures so that ablation in the PV region suppresses arrhythmogenic vagal responses. We reasoned that if PVs function primarily as drivers of cholinergic AF, their removal or disconnection from the LA should suppress vagal AF without affecting vagal responses elsewhere in the atria. On the other hand, if PV location adjacent to autonomic ganglia is critical, ablation directed at the ganglia should suppress vagal AF without affecting PV conduction. The present study was designed to distinguish between these possibilities.

Methods

General

Thirty adult mongrel dogs (weight, 20 to 40 kg) were studied in the following series: (1) effects on vagal AF in vivo of PV isolation (n=5) and of PV ostial ganglion ablation without PV isolation (n=7), (2) effects of PV excision in vitro on atrial cardiomyocyte electrophysiology and AF produced by carbachol at 100 (n=5) and 500 (n=5) nmol/L, (3) sham-ablation controls for time-related changes in ganglion ablation dogs (n=4), and (4) nonganglion ablation controls for mass of tissue ablated during PV ostial ablation (n=5). All animals were anesthetized (morphine 2 mg/kg SC; α-chloralose 120-mg/kg IV load, 29.25 mg · kg⁻¹·h⁻¹ maintenance) and mechanically ventilated according to a nomogram. Arterial blood pressure was monitored and hypotension was prevented by Ringer’s lactate infusion. Body temperature was maintained at 37±1°C with a homeothermic heating blanket.

In Vivo Studies

After median sternotomy, a pericardial cradle was created. Bipolar electrodes were hooked into right atrial (RA) and LA appendages. Cervical vagal nerves were isolated, transected, and instrumented with bipolar Teflon-coated stainless steel electrodes that were insulated except for the distal 1 to 2 cm. The nerves were stimulated bilaterally with 10-Hz, 0.2-ms stimuli and a voltage selected to produce a sinus cycle length of 1000 to 1200 ms. The right ventricle was demand paced at 80 bpm.

Atrial effective refractory period (ERP) was measured at the RA and LA appendages at varying basic cycle lengths with 10 basic 2-ms, 2× threshold current stimuli (S1), followed by a 2-ms, twice-threshold premature stimulus (S2) at 5-ms decrements. Changes were consistent across basic cycle lengths, so only data at a basic cycle length of 300 ms are shown. The longest S1-S2 failure to capture defined the ERP. AF was induced by burst pacing with 4× threshold, 4-ms stimuli. Any episode of AF lasting ≥20 minutes was considered sustained and was terminated by stopping vagal stimulation.

Ganglion-Sparing PV Circumferential Ablation

Continuous circumferential linear ablation lines at the PV ostia were created with a bipolar epicardial clamp (AtriCure, Cincinnati, Ohio) delivering 32.5 W power. For right-sided PV ablation, the clamp was directed from the right superior to the right inferior PVs. A dramatic rise in impedance indicating lesion completion required 10 to 30 seconds. An overlapping lesion was then applied from the right inferior toward the right superior PVs. Autonomic ganglia were identified before PV isolation, and the clamp was positioned distally to avoid damage to ganglia. After ablation with the clamp device, an ablation pen was used to destroy remaining zones through which conduction occurred, producing full isolation (4.6±1.6 sites per dog). If signs of vagal or sympathetic activation were observed during radiofrequency application, radiofrequency delivery was suspended, and the clamp was moved distally. A similar approach was used to isolate left-sided PVs. The order of PV isolation (right versus left side first) was randomized and did not affect outcome. Images from 1 dog before and after PV isolation are shown in Figure I of the online Data Supplement.

Each PV was mapped epicardially on 6 segments (anterior and posterior cranial, anterior and posterior caudal, ventral, dorsal) with a bipolar probe electrode for the presence of PV potentials during pacing from the LA appendage base. PV isolation was defined as a loss of PV response to LA stimulation and of LA response to PV stimulation at all PV sites distal to the ablation line.

Autonomic Ganglion Localization and Ablation

Fat pads containing autonomic ganglia were visible as pale white areas under the epicardial surface. Autonomic ganglia were localized by their response to high-frequency stimulation (20 Hz, 0.4-ms pulse width, current intensity half the atrial capture threshold) applied 0.5 to 1 mm subepicardially. A >20% decrease in sinus cycle length or induction of atrial tachycardia indicated an adrenergic response. Atrioventricular block, asystole, sinus bradycardia <40 bpm, and a mean RR interval increase >50% during AF were considered vagal responses. Peri-PV ostial ganglion regions were located up to 1 cm from right-sided PV ostia and up to 2 cm from left-sided ostia.

Radiofrequency ablation was delivered to autonomic ganglia via an epicardial ablation pen (35 W through a 100-Ω resistance). The order of left versus right-sided ganglion ablation was randomized. Successful ganglion ablation was defined by abolition of the heart rate response to high-frequency subthreshold stimulation at the same regions that had elicited clear responses before ablation. Transmural lesions were avoided, and there was no evidence of conduction block after ganglion ablation. Images from 1 dog before and after ganglion ablation are shown in Figure II of the Data Supplement. Two sets of control studies were performed for the ganglion ablation experiments. In 1 series, ganglia were localized in a manner identical to ganglion ablation experiments, and the response was reset after applications of the ablation pen without RF current. In the second series, multiple antral lesions were applied on the PV ostia in the same way as for ganglion ablation dogs in zones adjacent to but avoiding the ganglia. In this way, we mimicked the number and extent of lesions applied to the periostial ganglia without directly applying RF energy to the ganglia themselves.

Atrial Frequency Spectrum Analysis

Patch arrays were used to record atrial activity at 64 sites on either side of the atria during AF. The hexagonal patch measured 47×54 mm, with ~4 mm between bipolar electrode pairs evenly distributed across the array. The right-sided array covered the ventral surface of the RA and a small zone of LA tissue adjacent to right inferior and superior PVs. The left-sided array covered most of the lateral and posterior LA wall. QRS subtraction was used to remove QRS artifacts during AF. Fast Fourier transformation of digitized bipolar electrograms (60 000 points) was performed to analyze content in the 0.5- to 80-Hz band. The mean of each signal was first subtracted to make the signal zero mean. A split-cosine, bell-tapering window was applied, with 5% of data points being tapered. An estimate of the signal spectrum was obtained by using a smoothed periodogram with a smoothing parameter of (M). M was determined semiautomatically with an unbiased risk estimator method to choose the tuning parameter M in the smoothed periodogram method. The dominant frequency (DF) was defined as the frequency of the highest peak of the smoothed periodogram.

In Vitro Studies

Hearts were excised via left thoracotomy and immersed in oxygenated Tyrode’s solution. Tissue preparations, including the LA and
attached PVs, were mounted in a Plexiglas chamber and perfused via the left circumflex coronary artery with oxygenated Krebs’ solution at 36±0.5°C. Fine-tipped microelectrodes (resistance, 15 to 20 MΩ when filled with 3 mol/L KCl) coupled to a high-input impedance amplifier were used to record action potentials.16 LA action potential duration (basic cycle length, 500 ms) and AF duration were recorded before and during perfusion with carbachol at 100 and 500 nmol/L (n=5 per group). Carbachol was then washed out until baseline values returned; all PVs were surgically excised at their ostia; and measurements were repeated in the absence and presence of carbachol. Krebs’ solution contained (mmol/L) NaCl 120, KCl 4, KH2PO4 1.2, MgSO4 1.2, NaHCO3 25, CaCl2 1.25, and dextrose 5 (95% O2/5% CO2, pH 7.4).

Statistical Analysis

Continuous variables are expressed as mean±SEM. For comparisons involving single repeated measures only, paired t tests were used. For multiple repeated-measures comparisons with the same baseline, repeated-measures ANOVA was used, with Bonferroni-adjusted t tests to compare individual mean differences if ANOVA was significant. Categorical variables were compared with Fisher’s exact test. Two-tailed values of P<0.05 indicated statistical significance.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Electrophysiological Effects of Ganglion-Sparing PV Circumferential Ablation In Vivo

Figure 1A shows examples electrograms recorded from each of the PVs from 1 dog before and after PV isolation. PV isolation did not alter baseline ERP (Figure 1B) or the ERP response to vagal stimulation (Figure 1C). PV isolation failed to prevent sustained AF during vagal stimulation in any dog (Figure 1D).

Electrophysiological Effects of PV Excision In Vitro

To use an alternative method of evaluating the effects of PV removal on 2 levels of cholinergic AF promotion, we assessed the effects of surgically excising all the PVs in a previously characterized in vitro PV LA preparation.16 Figure 2A shows typical LA action potentials before and after exposure to 500 nmol/L carbachol, which greatly decreased action potential duration. Figure 2B shows examples of atrial activity induced by burst pacing in the absence and presence of carbachol. In the absence of carbachol, burst pacing induced only several repetitive responses. In the presence of carbachol, however, long-lasting runs of fibrillatory activity were readily induced. Figure 2C shows the mean action potential duration to 90% repolarization (APD90) –reducing effect of carbachol, which was quantitatively unchanged by PV excision. The bar graphs in Figure 2D show mean AF duration in the presence of 100 nmol/L carbachol (left) and the prevalence of sustained AF with 500 nmol/L carbachol.
vagal stimulation was unaffected by ablation of only right or left PV ganglia, whether measured on the side ipsilateral or contralateral to the ablation (Figure 3B). However, ablation of ganglia on both sets of PV ostia abolished the ERP response. The baseline ERP (in the absence of vagal stimulation) was increased slightly but significantly when measured on the same side as a unilateral ganglion ablation but was unaffected on the contralateral side (Figure 3C). Bilateral PV ostial autonomic ganglion ablation increased baseline atrial ERP significantly. In all dogs, vagal stimulation permitted sustained AF induction before ablation and after unilateral ablation of the left or right PV ostial ganglia (Figure 3D). However, after ablation of the ganglia at the base of both left- and right-sided ostia, sustained AF could not be induced during cervical vagal nerve stimulation, and mean AF duration during vagal stimulation averaged $92 \pm 21$ seconds.

**DF Analysis**

To gain insights into the success and failure of various in vivo interventions, we performed DF analysis as illustrated for ganglion-sparing PV circumferential ablation in Figure 4. Each panel shows electrogram recordings during vagal AF from the site with the largest DF ($DF_{max}$), its frequency spectrum, and a color-coded DF distribution map for the right-sided (top) and left-sided (bottom) mapping surfaces. In the dog illustrated in Figure 4, the RA $DF_{max}$ was greater than the LA $DF_{max}$ under baseline conditions (left). After isolation of the left-sided PVs, the LA $DF_{max}$ was reduced slightly, and activity became somewhat more fragmented, but the RA $DF_{max}$ was not changed (middle). After subsequent isolation of the right-sided PVs, the RA $DF_{max}$ was slightly decreased, and zones of slower activation (yellow, DF of 15 to 20 Hz; green, DF <10 Hz) appeared, but there were still large zones of very rapid activation (DF >30 Hz), whereas no further change occurred in LA activation.

Figure 5A shows mean DF data for all studies of ganglion-sparing PV isolation. At the left are values for mean DF at all right- and left-side recording sites before and after bilateral ablation. Overall, mean DF was significantly reduced for right-sided sites but was not affected in the left-sided ones. At the right are corresponding mean values for $DF_{max}$ before and after ablation. These were not significantly affected by bilateral ganglion-sparing PV circumferential ablation, suggesting that the failure of this procedure to affect vagal AF persistence was due to its inability to eliminate high-frequency regions that drive atrial activity during AF.

Figure 6 illustrates the results of DF analysis for 1 dog subjected to PV ostial ganglion ablation. Before ganglion ablation, very rapid activity was recorded over the RA during vagal AF (top left), with a $DF_{max}$ of ~28 Hz. The LA showed more fragmented electrograms with a $DF_{max}$ of ~14 Hz (bottom left). Ablation of left PV ostial ganglia reduced both RA and LA DFs, leaving $DF_{max}$ values of ~17 and ~8 Hz, respectively (middle). When the right PV ostial ganglia were then ablated, atrial activation slowed considerably (right), and AF was no longer sustained. Mean results for DF analysis of the response to PV ostial ganglion ablation are shown in Figure 5B. Mean DF over all sites on each side (left) was...
significantly reduced by ablation of the autonomic ganglia over PV ostia on the same side (unilateral ablation) and decreased further with bilateral ganglion ablation. The $DF_{\text{max}}$ on each side tended to decrease with unilateral ablation but remained on the order of $\approx 15$ Hz in at least 1 atrium after either right or left ganglion ablation (Figure 5B). After bilateral ablation of PV ganglia, both RA $DF_{\text{max}}$ and LA $DF_{\text{max}}$ were substantially and significantly decreased, averaging $<10$ Hz for each.

**Stability of the In Vivo Model**

In sham-ablation experiments, baseline ERPs and vagal ERP responses remained constant from beginning (before) to end (after) of all sham-ablation procedures (Figure 7A and 7B). Sustained vagal AF was induced in all 4 sham-ablation dogs throughout the experiment (Figure 7C). In addition, the heart rate response to subthreshold high-frequency ganglion stimulation was unchanged by sham ablation. These observations exclude time-related changes and the multiple high-frequency subthreshold stimulations required to identify the ostial ganglia as a cause of the loss of vagal response and AF during ganglion ablation experiments. Figure 7D through 7F shows corresponding results for the ostial nonganglion ablation experiments, which controlled for the tissue damage caused by ganglion ablation. Nonganglion ablation sites are shown in Figure 3A (bottom). Periostial ablation avoiding the ganglia was applied at 7.5±0.6 sites in nonganglion ablation dogs (versus 8.6±0.6 sites in ganglion ablation dogs; $P=\text{NS}$, nonpaired $t$ test) and did not significantly affect ERPs, the response to vagal stimulation, or the ability to induce sustained vagal AF.

**Discussion**

In the present study, we assessed the role of the PV region in vagal AF by targeted and separate removal of each of the components that may contribute: the PVs themselves and the autonomic ganglia adjacent to PV ostia. Our results suggest that it is PV-associated ganglia, not PVs themselves, that are important in vagally mediated AF promotion.
Pathophysiology of Vagal AF and Potential Role of the PVs

The AF-promoting properties of vagal activation have long been recognized. Vagal nerve discharge strongly abbreviates atrial refractoriness in a spatially heterogeneous way, producing a substrate that is very propitious for AF. Rapidly activating driver regions play a key role in maintaining vagal AF, and as few as 1 rapidly discharging rotor may be sufficient to maintain fibrillatory activity during cholinergic AF. The PVs play a key role in clinical AF and have cellular electrophysiological properties that favor reentry. Combined with the evidence that autonomic activation promotes PV arrhythmogenesis, the PVs themselves might reasonably be expected to be key drivers during vagal AF. Our results argue strongly against this possibility. There is substantial evidence that rapidly firing drivers with fast DFs maintain cholinergic AF. Our results are completely consistent with this notion; PV-directed ablation and unilateral ganglion ablation failed to significantly alter maximal DF<sub>max</sub> values and failed to prevent vagal AF. Only ablation of the ganglia adjacent to both sets of PVs significantly reduced DF<sub>max</sub> in both RA and LA (Figure 5) and suppressed vagal AF (Figure 3D).

Role of Autonomic Ganglia at the PV Ostia

The heart has an intrinsic autonomic nervous network, with intracardiac ganglia playing an important role in integrating and responding to autonomic nervous system and electromechanical stimuli. The ganglia sit in extracardiac fat pads on the epicardial surfaces, some of which are directly adjacent to PV ostia, and mediate important components of cardiac autonomic function. Stimulation of ganglionated plexuses near the PV ostia promotes AF by accelerating activity in nearby driver regions. As early as 1995, evidence was presented to support a role for vagal denervation in the efficacy of AF ablation procedures based on the effects of multiple epicardial lesions on vagal AF in the dog. Subsequently, Schauerte et al showed that catheter radiofrequency ablation delivered via the pulmonary arteries suppresses the effects of vagal nerve stimulation in dogs. In agreement with our findings, Razavi et al reported that catheter-based PV ablation substantially blunts the response to vagal nerve stimulation in dogs. In the present study, we observed prominent suppression of vagal responses with epicardial ablation directed at autonomic ganglia at the PV ostia identified on the basis of autonomic responses to high-frequency subthreshold stimulation.
Novelty and Potential Significance

There is substantial evidence for an important effect of PV ablation on the vagal AF. Two explanations for the role of the PV region in vagal AF are possible: a key role of PV tissue in the generation of vagally mediated arrhythmias and/or a role of autonomic ganglia adjacent to PVs that are eliminated by PV-directed ablation procedures. This study was designed to determine the contribution of each component in the canine model of vagal AF. Using complementary in vivo and in vitro approaches, we show that intact PVs connected electrically to the LA are not necessary for the maintenance of cholinergic vagal AF, whereas the destruction of autonomic ganglia adjacent to PV ostia strongly suppresses vagal AF.

There is evidence that vagal denervation contributes to the efficacy of LA circumferential ablation. Selective vagal denervation without PV isolation can prevent AF recurrence in patients with vagal AF. Epicardial fat pad ablation is followed by delayed reinnervation in dogs. Clinically, segmental and circumferential PV ablation produces vagal denervation; however, reinnervation is evident within 1 month of segmental PV ablation, whereas there is no evidence of reinnervation for at least 1 year after circumferential PV ablation. These findings may account in part for the superiority of circumferential PV ablation in preventing AF recurrence in some patient populations and for the observation that complete lines of block around the PVs may not be essential for success with the circumferential procedure. Segmental PV ablation combined with a vagal denervation procedure is more effective than segmental ablation alone in the treatment of paroxysmal AF.

Our results provide novel information regarding the mechanistic role of the PV region in vagal AF. They also support efforts directed at targeting atrial autonomic ganglia in AF therapy. These ganglia are situated on the epicardial surface of the heart, and epicardial ablation may prove to be more effective than endocardial procedures for autonomic denervation.

Potential Limitations

Our DFmax analysis was limited by the fact that we were not able to access all atrial sites (e.g., the septum was not accessed by our electrode arrays). Nevertheless, we were able to demonstrate a strong correlation between the ability to eliminate all high-frequency driver sites and the success of PV region–directed ablations.

Our results specifically examined the role of the PVs and PV ostia–associated ganglia in an experimental model of vagal AF. These results are relevant to vagal AF and should not be extrapolated directly to other forms of AF. The available evidence does suggest that intact vagal innervation may contribute to the maintenance of other forms of AF that do not strictly fall into the “vagal AF” category; however, further work is needed to assess the potential contribution of autonomic ganglia near the PV ostia to these other forms. The PV antrum actually may possess arrhythmogenic potential similar to tubular portions of the PVs. Therefore, we cannot exclude the possibility that vagally mediated AF depends on PV-type arrhythmogenicity originating in the antrum.

Our canine model involves a pure, vagally induced AF substrate that always requires atrial extrastimuli or burst pacing to induce AF. Clinical vagal AF is likely more complex, with an interaction between initiating triggers (that likely come from PVs) and a vagally facilitated AF-maintaining substrate. The fact that PV driver foci are not as important in clinical vagal AF as in other forms is suggested by the lower efficacy of PV isolation in vagal AF (≈50%) compared with other forms. When PV-directed ablation is effective in clinical vagal AF, the positive response may result from ablation of PV ostial ganglia and/or PV foci that act on the vagally induced vulnerable substrate for AF maintenance. Our model is more relevant to vagotonic AF-maintaining mechanisms than to initiators. In addition, clinical experience indicates an uncommon role for RA AF perpetuators. Therefore, extrapolation from our model to clinical AF should be done cautiously.

Conclusions

The presence of intact PVs is not needed for vagal AF maintenance. Ablation of the autonomic ganglia near the PV ostia strongly blunts the effects of vagal activation, decreases the activation frequency, and prevents the maintenance of vagal AF.

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Disclosures

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**CLINICAL PERSPECTIVE**

Ablation procedures directed at the pulmonary vein (PV) region have had a very important impact on the management of atrial fibrillation (AF). PV-directed procedures initially targeted highly localized arrhythmogenic PV foci but now focus on larger lesions that isolate the PVs by encompassing the PV ostia and are effective in a broader range of patients. Vagal discharge is a strong AF promoter in humans and experimental models, and PV-directed procedures can be effective in AF cases with particular dependency on vagal tone (vagal AF). There is evidence from animal models of vagal AF that PVs may act as “drivers” that maintain AF. On the other hand, there also are autonomic ganglia near the PV ostia. Thus, there are 2 potential mechanisms for efficacy of PV-directed procedures in vagal AF: elimination of AF-maintaining PV drivers and damage to autonomic ganglia that act as essential vagal “relay stations.” We assessed these mechanisms by targeted ablation in canine models of vagal AF. Eliminating potential PV drivers by isolating or removing the PVs did not prevent AF maintenance during vagal activation. On the other hand, ablation of the autonomic ganglia near the PV ostia suppressed vagal effects and made it impossible for AF to sustain itself in the presence of strong vagal nerve stimulation. Thus, it appears that the PVs are not essential for AF maintenance in the presence of strong vagal tone and that ablation of autonomic ganglia near PV ostia may be an important contributor to the efficacy of PV-directed ablation procedures in some types of AF.
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