Catheter Ablation of Cardiac Autonomic Nerves for Prevention of Vagal Atrial Fibrillation

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Background—Vagal stimulation shortens the atrial effective refractory period (AERP) and maintains atrial fibrillation (AF). This study investigated whether the parasympathetic pathways that innervate the atria can be identified and ablated by use of transvenous catheter stimulation and radiofrequency current catheter ablation (RFCA) techniques.

Methods and Results—In 11 dogs, AERPs were determined at 7 atrial sites during bilateral cervical vagal nerve stimulation (VNS) and electrical stimulation of the third fat pad (20 Hz) in the right pulmonary artery (RPA). VNS shortened the AERP at all sites (from 123±4 to 39±4 ms, P<0.001) and increased the covariance of AERP (COV-AERP) (from 9±3% to 27±13%, P<0.001). RPA stimulation shortened the AERP at all sites from 123±4 to 66±13 ms (P<0.001) and increased the COV-AERP from 9±3% to 30±12% (P<0.001). In 7 dogs, transvascular RFCA of the parasympathetic pathways along the RPA was performed, and in 3 dogs, additional RFCA of parasympathetic fibers along the inferior (n=2) or superior (n=1) vena cava was performed. RFCA blunted the AERP shortening at all sites during VNS (114±4 ms after RFCA), abolished the increase of COV-AERP during VNS (12±7% after RFCA), and led to an increase of the baseline AERP (123±4 ms before versus 127±3 ms after RFCA, P=0.002). Before RFCA, AF could be induced and maintained as long as VNS was continued, whereas after RFCA, AF was no longer inducible during VNS.

Conclusions—Transvascular atrial parasympathetic nerve system modification by RFCA abolishes vagally mediated AF. This antifibrillatory procedure may provide a foundation for investigating the usefulness of neural ablation in chronic animal models of AF and eventually in patients with AF and high vagal tone. (Circulation. 2000;102:2774-2780.)

Key Words: fibrillation • electrophysiology • ablation • nervous system, autonomic

Parasympathetic stimulation has for decades been used for the induction and maintenance of atrial fibrillation (AF) in experimental protocols.1,2 Parasympathetic stimulation dramatically shortens the atrial effective refractory period (AERP), thereby decreasing the wavelength of atrial excitation wave fronts.3 The shorter the wavelength, the higher is the probability that multiple reentrant circuits can exist simultaneously in the atrial myocardium; the presence of these multiple circuits, in turn, increases the stability of AF.4 Clinical evidence for a role of the parasympathetic nervous system in human AF has been provided by observations of Coumel5 and Chen et al.6 The purpose of the present study was 2-fold. First, we wished to determine whether transvascular electrical stimulation with a catheter can be used to identify the location of the parasympathetic nerve fibers that innervate the atria. Second, we evaluated the efficacy of transvascular radiofrequency catheter ablation of these nerves to parasympathetically denervate the atria.

Methods

Surgical Preparations

All animal studies were approved by the Research and Development Committee of the Department of Veterans Affairs Medical Center, Oklahoma City, Okla. In 11 mongrel dogs (18 to 23 kg), anesthesia was performed with sodium pentobarbital (initial bolus 30 mg/kg IV, 50 to 100 mg as needed for maintenance). The dogs were ventilated with room air (Harvard Apparatus Co). After right lateral thoracotomy, the heart was exposed in a pericardial cradle. Multielectrode catheters (Cordis Webster Corp) were sutured to the left superior pulmonary vein, the Bachmann’s bundle, the right atrial appendage (RAA), and the low right atrium (LRA). Another multielectrode catheter was inserted into the coronary sinus. Surface ECG lead II/aVR and intracardiac tracings were recorded by use of a Bard Labsystem (CR Bard Inc).

Parasympathetic Autonomic Nerve Stimulation

For cervical vagal nerve stimulation (VNS), the cervical vagosympathetic trunks were cut, and silver wires were introduced in the cranial end of the vagosympathetic trunk. Rectangular electrical stimuli were delivered at a frequency of 20 Hz and a pulse duration of 2 ms (Grass stimulator S-88, Astro Med Inc, Grass Instruments Division). The voltage chosen for right (left) VNS was 5 V above the voltage at which sinus arrest lasting >2 seconds (complete atrioventricular [AV] block) was achieved. These stimulation strengths were also applied during bilateral VNS and were kept constant during the experiment.

For stimulation of cardiac parasympathetic nerves in the right pulmonary artery (RPA), a basket catheter (Cordis Webster Corp, Aachen, Germany). E-mail psch@pcserver.mk1.rwth-aachen.de

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predominantly innervate the AV node but also parts of the atria.8,9 and the ostium of the coronary sinus. This fat pad has been shown to be located in fat pad between the inferior right atrium, the IVC, and the ostium of the coronary sinus (**), and along SVC. Stimulation and ablation of parasympathetic nerves was performed with expandable electrode catheter, which was introduced into upper RPA (n=7), SVC (n=1), or IVC (n=2).

Figure 1, which consisted of a 7F shaft with an expandable basket-shaped electrode array at its end, was used. The basket consisted of 5 metal electrode arms. Bipolar electrical stimulation could be performed between adjacent arms of the basket (stimulation frequency 20 Hz, pulse duration 0.1 ms; Grass stimulator S-88, Astro Med Inc, Grass Instruments Division). The basket catheter was introduced into the proximal RPA under fluoroscopic guidance. To identify an intravascular site in the RPA at which parasympathetic cardiac nerves could be stimulated, the slowing of the sinus rate during stimulation over each pair of electrode arms at 35 V was measured. This sinus rate slowing has previously been shown to be mediated by parasympathetic cardiac nerves.7 If no noticeable rate slowing occurred during stimulation over each pair of splines, the basket was contracted and gradually advanced or withdrawn within the RPA until a site with a visible sinus rate slowing was found. To ascertain that the stimulation/ablation site in the RPA was distant from the atrium, we confirmed that the atria could not be paced from the RPA. For this purpose, pacing stimuli at cycle lengths of 400 to 500 ms were delivered with 35 V (pulse duration 2 ms) in the RPA each time before high-frequency electrical stimulation/ablation was started in the RPA.

In 2 dogs, transvascular parasympathetic stimulation (TPS) was performed at the border of the inferior vena cava (IVC) to the right atrium opposite a fat pad between the inferior right atrium, the IVC, and the ostium of the coronary sinus. This fat pad has been shown to predominantly innervate the AV node but also parts of the atria.8,9 Stimulation (20 Hz, pulse duration 0.1 ms) in the IVC excited atrial tissue, resulting in AF, which terminated immediately after cessation of electrical stimulation. However, besides exciting atrial tissue, TPS caused a ventricular rate slowing effect during AF, as described previously.10 The presence of such ventricular rate slowing during AF was taken as an indication that the basket catheter was positioned adjacent to the parasympathetic fat pad.

Measurement of AERPs and AV Conduction
AERPs at 7 atrial sites were measured at baseline during unilateral or bilateral VNS and during TPS in the RPA by use of the extrastimulus technique (basic cycle length 300 ms, final extrastimulus steps 1 ms) and pacing stimuli at twice the diastolic pacing threshold. The longest coupling interval that did not capture the atria was defined as AERP.

To assess the heterogeneity of the AERPs, we calculated the coefficient of variation of the AERP (COV-AERP=standard deviation/mean×100%) at the 7 atrial sites in each dog. An increased COV-AERP has been demonstrated to be strongly correlated with atrial vulnerability to AF.11 AV conduction was evaluated by incremental pacing from the RAA until Wenckebach type 2 AV block occurred.

Ganglionic Blockade
In 4 animals, AERP determinations during VNS or TPS in the RPA were performed before and after the infusion of hexamethonium chloride (bolus injection 7.6 mg/kg body wt, maintenance infusion 0.76 mg/kg body wt per minute; Sigma Chemical Co), a nicotinergic ganglionic blocking agent.

Radiofrequency Current Ablation
Delivery of radiofrequency current occurred in a unipolar mode between one of the splines and a cutaneous patch electrode. By contrast, electrical stimulation of parasympathetic nerves was performed in a bipolar fashion over adjacent splines of the basket catheter. Therefore, with the applied catheter, we were not able to identify a single spline but a pair of splines that revealed maximum response to high-frequency stimulation. For ablation, radiofrequency current was first delivered to 1 of the 2 splines of the electrode pair with maximal response to high-frequency stimulation. If there was still a shortening of the AERP during VNS and stimulation over the pair of splines of the basket catheter after the first ablation attempt, the second of the 2 splines was chosen for radiofrequency current ablation (RFCA). Radiofrequency current was delivered at 520 kHz/70 V for 60 seconds (American Cardiac Ablation Corp).

Statistical Analysis
All data are expressed as mean±1 SD. AERPs and cycle lengths at which 2:1 AV nodal block occurred were compared by means of a Student paired t test. Values of P<0.05 were considered significant.

Results

Cervical VNS
During supramaximal bilateral VNS, the AERP at all 7 atrial sites shortened from 123±4 ms at baseline to 39±4 ms (P<0.001; n=11). The percentage of AERP shortening at each of these 7 atrial sites is illustrated in Figure 2. Bilateral VNS also increased AERP heterogeneity as measured by COV-AERP (9±3% without versus 27±13% with bilateral VNS, P<0.001; n=11).

Transvascular Parasympathetic Stimulation
TPS in the RPA significantly shortened the AERP at all 7 atrial sites from 123±4 ms at baseline to 66±13 ms (P<0.001; n=11, Figure 3). TPS in the RPA also increased the AERP heterogeneity (COV-AERP 9±3% at baseline versus 30±12% during TPS in the RPA, P<0.001; n=11). During TPS in the RPA, AF could be induced with a single extrastimulus at each of the 7 atrial sites and could be maintained as long as RPA stimulation was continued. By contrast, without TPS in the RPA, the induction of AF during programmed stimulation was rare. RPA stimulation also significantly increased the supraventricular cycle length from 400±88 ms (n=11) at baseline to 870±342 ms during TPS (n=10, P<0.001) and led to a sinus node arrest in 1 animal. There was a significant prolongation of the antegrade Wenckebach cycle length during RPA stimulation (187±24 ms at baseline [n=11] versus 297±117 ms during TPS in the RPA [n=8]). In 3 animals, TPS in the RPA caused a complete AV block.
Intravenous infusion of hexamethonium chloride in 4 dogs completely abolished the AERP shortening at all 7 atrial sites during bilateral VNS and TPS in the RPA (123±6 ms for baseline AERP versus 53±22 ms during TPS in the RPA before hexamethonium \( P<0.001 \) and versus 122±5 ms during TPS in the RPA after hexamethonium \( P=\text{NS} \)). Also, intravenous injection of 3 mg atropine prevented the induction of sustained AF during programmed stimulation and bilateral VNS or TPS in the RPA.

In those 2 dogs in which RFCA was performed in the IVC, high-frequency stimulation in the IVC before RFCA led to a marked decrease of the ventricular rate during AF (RR interval was 884±392 ms with TPS versus 221±33 ms without TPS).

**Effect of Transvascular Atrial Parasympathetic Nerve System Modification on AERPs**

Transvascular RFCA of atrial parasympathetic nerves was performed in 7 dogs. In 4 dogs, RFCA was restricted to the RPA, whereas in 1 dog, ablation was performed in the RPA and the superior vena cava (SVC). In 2 dogs, ablation was performed in the RPA and in the IVC close to the right atrium. Importantly, at the ablation sites in the RPA and in the SVC, electrical capture (pacing) of atrial myocardial tissue never occurred before and after ablation even at the highest possible stimulation voltage. Similarly, electrical high-frequency stimulation in the RPA never induced AF unless simultaneous programmed atrial stimulation was performed. On average, 9±4 RFCA with an impedance of 178±64 \( \Omega \) was delivered in each animal. The end point of RFCA was the noninducibility of sustained AF (>20 seconds) with a single atrial extrastimulus during supramaximal bilateral VNS.

Intravascular RFCA of atrial parasympathetic nerves significantly diminished the AERP shortening that was due to supramaximal bilateral VNS at all 7 atrial sites (Figures 4 and 5). Transvascular RFCA of atrial parasympathetic nerves also led to a significant increase of the baseline AERP at all 7 sites (from 123±4 ms before ablation to 127±3 ms after ablation, \( P=0.002 \); \( n=7 \), Figure 4). Before ablation, AF could be easily induced and maintained for >1 hour at each of the 7 atrial sites during bilateral VNS and programmed atrial stimulation with a single extrastimulus, whereas after ablation, sustained AF was no longer inducible during simultaneous bilateral VNS at any of the 7 atrial sites despite aggressive rapid atrial burst pacing (10 seconds with 10 Hz). The heterogeneity of the baseline AERPs did not differ significantly before RFCA (COV-AERP 9±3%) and after RFCA (COV-AERP 8±3%). By contrast, the increase of AERP heterogeneity during bilateral VNS was almost abolished after ablation (COV-AERP during bilateral VNS was 30±14% before ablation versus 12±7% after ablation; \( P=0.02 \)).

In 1 dog, after ablation in the RPA, an AERP shortening during bilateral and right VNS was still present at the RAA and LRA, and sustained AF remained inducible. In this dog, TPS was performed in the SVC, 3 cm above its junction with the right atrium, where a considerable decrease of the AERP at the RAA and LRA was obtained during TPS. After application of one RFCA pulse in the SVC, the AERP shortening during VNS was abolished, and AF was rendered noninducible during VNS. In 2 dogs, additional RFCA was performed in the IVC. In 1 dog, the AERP at the proximal Bachmann’s bundle and LRA still shortened during bilateral or right VNS, and sustained AF was inducible. Application of 3 RFCA pulses to the IVC
current applications to the same spline at the same location and 1 current application to the second spline) blunted this AERP shortening, and sustained AF became noninducible. In the second dog, left and bilateral VNS still considerably shortened the AERP at the distal coronary sinus, and sustained AF remained inducible. After application of one radiofrequency current pulse to the IVC, VNS no longer decreased the AERP at the distal coronary sinus, and AF became noninducible.

Effect of Transvascular Atrial Parasympathetic Nerve System Modification on Sinus Rate and AV Conduction
After ablation, bilateral VNS no longer significantly decreased the sinus rate (AA intervals were 440±123 ms without VNS versus 405±92 ms with bilateral VNS) or prolonged the antegrade Wenckebach cycle length (191±31 ms with VNS and 185±28 ms without VNS). The baseline sinus rhythm cycle length did not change significantly before (409±102 ms) and after (440±123 ms) ablation. Similarly, no significant change of the baseline antegrade Wenckebach cycle length was observed before (185±28 ms) and after (203±38 ms) ablation. After ablation at the IVC, the negative dromotropic effect during TPS in the IVC was abolished.

Histopathology
Macroscopic postmortem inspection of the ablation sites in the RPA and SVC showed linear lesions of 5 to 10 mm but did not reveal visible intravascular thrombi attached to these lesions (Figure 6). The RFCA lesions were found to be located at the floor and the ventrolateral wall of the proximal RPA. In 2 dogs in which ablation was performed in the IVC, macroscopic lesions (length 3 to 4 mm) were observed at the posterior and left lateral aspect of the IVC at its transition to the right atrium. Histological sections showed various nerves in the fibrous and fatty tissue surrounding the RPA (Figure 7). After ablation in the RPA, a hemorrhagic exudate and a polymorphic infiltrate could be seen around the nerves in the fibrous and fatty tissue surrounding the RPA opposite the intravascular ablation lesion. Macroscopic inspection and histological examinations of the atria of dogs that were ablated exclusively in the RPA did not reveal signs of atrial damage after the ablation procedure.

Discussion
The present study demonstrates how the major parasympathetic pathways to the atria can be identified by use of a catheter-based transvenous approach. The results further show that intravascular RFCA of these parasympathetic nerves can be achieved; this ablation almost completely abolished the AERP shortening and the increased AERP

Figure 4. Effect of bilateral cervical VNS on AERPs at all 7 atrial stimulation sites before and after RFCA. RFCA almost abolished AERP shortening during cervical VNS and led to a significant increase of baseline AERP after RFCA. *P<.001 vs baseline.

Figure 5. AERP shortening during bilateral supramaximal cervical VNS before and after ablation. *P<.001 vs before ablation. Abbreviations as in Figure 2.
heterogeneity during bilateral VNS and prevented the induction and maintenance of AF during VNS. A surgical technique for atrial parasympathetic denervation requiring a thoracotomy was originally developed by the elaborate studies of Kaye, Randall, and colleagues \(^{12,13}\) and was later modified by Chiou et al. \(^9\)

Several clinical observations have suggested that an increased parasympathetic tone is involved in the genesis of at least some forms of paroxysmal AF. \(^5,6\) However, the role of the parasympathetic nervous system in chronic AF is less clear. In atrial biopsies obtained from patients with chronic AF, the acetylcholinesterase activity was shown to be significantly reduced compared with the activity in patients with sinus rhythm. \(^14\) Therefore, a lower inactivation rate of acetylcholine might account for a higher vagal tone in some patients with chronic AF. \(^14\)

Parasympathetic stimulation shortens the AERP and decreases the wavelength of atrial reentrant circuits. \(^3\) Besides shortening the AERP, vagal stimulation increases the AERP dispersion, which in turn contributes to the stability of AF. \(^2,15–17\) Although the exact role of the parasympathetic nervous system in chronic AF is not clear at present, it seems reasonable to speculate that some of the electrophysiological changes during chronic AF (ie, decrease of the AERP and increase of the AERP dispersion) may be at least potentiated by the parasympathetic nervous system.

Possible Clinical Implications

Clinical implications of the proposed approach for transvascular atrial parasympathetic nerve system modification must be considered cautiously until chronic animal studies determine that no relevant autonomic reinnervation or RPA stenosis will occur after the procedure. Nevertheless, potential target groups for such an approach will be discussed briefly as detailed below.

Coumel and colleagues \(^5,18\) and later Chen et al\(^6\) have described subgroups of patients with paroxysmal AF with an augmented parasympathetic tone. In these patients, antiarrhythmic agents such as flecainide or amiodarone can successfully reduce the frequency of AF paroxysms. In some patients who are resistant to amiodarone and/or flecainide, atrial pacing alone or in addition to antiarrhythmic drugs is very effective in preventing these arrhythmias. Atrial pacing very consistently prevents vagally induced AF, thus showing that it is at least partly bradycardia dependent rather than
vagally induced. Several examples of this phenomenon are given by the thorough clinical studies of Coumel and colleagues.\textsuperscript{5,18} The present study suggests that for some AF patients with an elevated vagal tone, transvenous parasympathetic nerve system modification may be developed as an alternative treatment modality. Interestingly, this procedure also significantly blunted the sinus rate slowing during VNS. Although the outcome is speculative, one could imagine that in patients with vagal AF, the proposed ablation procedure could blunt both a vagally dependent sinus bradycardia and a vagally induced shortening of the AERP. However, the long-term safety and feasibility of the ablation procedure must be demonstrated in animals before any recommendations for the treatment of patients with such an ablation procedure are justified.

Even in AF patients with no obvious clinical evidence of an elevated parasympathetic tone, the prolongation of the baseline AERP after intravascular atrial parasympathetic nerve system modification may have an antiarrhythmic effect. Although significantly so, this baseline AERP prolongation after ablation was relatively small in the present study. However, it has must be taken into account that the pentobarbital anesthesia leads to an almost total loss of the resting vagal tone.\textsuperscript{19} Thus, it is conceivable that the AERP prolongation after ablation may in fact be greater with a different kind of anesthesia or without anesthesia.

Last, but not least, the Maze procedure for the treatment of AF partially parasympathetically denervates the atria, as recently shown by Elvan.\textsuperscript{20} Similarly, Chevalier et al\textsuperscript{21} demonstrated that linear atrial myocardial lesions applied epicardially to the atria via thoracoscopy significantly decreased the inducibility of vagally induced and maintained AF. However, the cited and other approaches for the Maze procedure differ significantly from the ablation procedure described in the present study because they all apply linear atrial myocardial tissue lesions. By contrast, in the majority of cases of the present study, lesions were created in the great vessels outside the heart proper. If a parasympathetic denervation contributes to the success of the Maze procedure, the question arises as to whether transvenous atrial parasympathetic nerve system modification as described in the present study may reduce the required number of linear lesions of a Maze procedure.

Study Limitations

Transvenous atrial parasympathetic nerve system modification also abolished the vagal prolongation of the sinus cycle length and AV conduction during bilateral VNS. Theoretically, this could increase the ventricular rate if AF should recur after the ablation procedure. We did not test whether the sympathetic innervation of the sinus and AV node was still preserved after ablation. However, previous studies have already shown that surgical dissection of the parasympathetic nerves providing the atria and the AV and sinus nodes does not significantly affect the sympathetic innervation of these structures.\textsuperscript{13,22} Therefore, a neural and humoral sympathetic modulation of the sinus rate and AV conduction may still be possible after ablation. In fact, a slight increase of the sinus rate during bilateral stimulation of the vagosympathetic trunk after ablation may be taken as an evidence that the sympathetic innervation of the sinus node is at least partly preserved.

In the present study, we did not seek to determine whether the parasympathetic nerves at the RPA, IVC, and SVC sites also innervate the ventricles. However, we did not observe a significant change in the ventricular refractory periods during RPA stimulation in previous studies.\textsuperscript{7,23} Similarly, other authors have previously shown that epicardial destruction of the parasympathetic fat pads adjacent to the RPA and IVC did not affect the prolongation of the ventricular refractory period that was due to bilateral VNS.\textsuperscript{24}

In this acute animal model, ablation in the RPA led to circumscript noncircumferential lesions in the RPA. Macroscopic thrombosis at the ablation sites was not observed although the dogs were not anticoagulated. However, it is possible that ablation in the RPA may cause pulmonary embolism or pulmonary stenosis in the long term.

There may be concerns as to whether the ablation effect in the present study was due to a nonspecific atrial ablation effect rather than modification of the parasympathetic nerves. It should be emphasized that in 5 of the 7 dogs, RFCA was restricted to the RPA (n=4) or RPA and SVC (n=1). In these dogs, ablation was performed without an atrial entrance of the catheter. At the ablation sites in the RPA and in the SVC, electrical capture (pacing) of atrial myocardial tissue never occurred before or after RFCA. Rather, programmed atrial stimulation from the 7 atrial testing sites could be performed for AERP determination during nerve stimulation in the RPA and SVC. This is a strong evidence that the ablation effect at least in the majority of animals was not due to a destruction of atrial myocardial tissue. This is further supported by the fact that macroscopic inspection and histological examinations of the atria of the dogs that were ablated exclusively in the RPA did not reveal signs of atrial damage after the ablation procedure.

In 1 animal, however, in addition to the RPA lesions, a single RFCA lesion (macroscopic length 4 mm, width 2 mm) was created at the posterior left lateral quadrant of the IVC at its transition to the right atrium. In a second dog, 2 lesions (average length 4 mm) were created at the posterior and left lateral aspect of the IVC at its transition to the right atrium in addition to the RPA lesions. Therefore, in these 2 dogs, we cannot exclude that in addition to the ablation lesions outside the heart (in the RPA), an atrial myocardial ablation effect may have contributed to the noninducibility of vagal AF. Importantly, the atrial lesions in the IVC abolished the shortening of the AERP during bilateral VNS at atrial sites distant from the ablation site; this finding indicates that an neural ablation effect was also operating. Moreover, from earlier experiments in which pharmacological nerve blockade with atropine or hexamethonium diminished the negative dromotropic effect of high-frequency stimulation in the IVC,\textsuperscript{10} it is conceivable that parasympathetic nerves were stimulated at the IVC/right atrial site in these 2 dogs.

Conclusions

Parasympathetic nerves innervating most of the atria can be stimulated and ablated in the RPA, IVC, and SVC by use of
a transvenous catheter technique. Neural ablation abolishes vagal AF. Further testing of this antifibrillatory procedure in chronic animal models of AF is essential if transvenous parasympathetic atrial modification is to have clinical utility.

References

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