Combined Effect of Pulmonary Vein Isolation and Ablation of Cardiac Autonomic Nerves for Atrial Fibrillation

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SUMMARY

This study was designed to determine whether endocardial high-frequency stimulation at the pulmonary vein (PV) antrums can localize cardiac autonomic ganglionated plexi (GP) and whether ablation at these sites can evoke a vagal response and provide a long-term benefit after PV isolation (PVI) for atrial fibrillation (AF).

Radiofrequency ablation of each PV antrum was performed in 21 patients with paroxysmal AF (n = 17) or persistent (n = 4) AF. In 8 patients with paroxysmal AF, a ring electrode catheter was placed at each PV antrum. High-frequency stimulation prolonged the R-R interval in 6 of 8 patients at the left superior (LS) PV, in 3 of 8 patients at the left inferior (LI) PV, in 3 of 8 patients at the right superior (RS) PV, and in 3 of 8 patients at the right inferior (RI) PV. A decrease in sinus rate > 20% was observed in 4 of 21 patients during LS PVI, in 2 of 21 patients during RS PVI, and in 1 of 2 patients during RI PVI. Atrioventricular block or a > 5 second pause was observed in 5 of 21 patients during LS PVI. AF recurred during the follow-up period in 5 of the 16 patients (31%) who had no atrioventricular block or > 5 second pause during PVI but did not recur in 5 patients in whom atrioventricular block or a > 5 second pause developed during PVI.

GP can be identified by endocardial stimulation. The AF recurrence rate is decreased when a vagal response is achieved by radiofrequency ablation. (Int Heart J 2008; 49: 661-670)

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A description of the intrinsic cardiac nervous system in humans by Armour, et al1) raised the question of whether autonomic inputs from the ganglionated plexi

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(GP) that surround the heart contribute to both the initiation and maintenance of atrial fibrillation (AF). High-frequency stimulation of epicardial autonomic plexi can induce triggered activity from the pulmonary veins (PVs)\(^3\) by acetylcholine-induced shortening of action potential duration and by a transient norepinephrine-induced increase in calcium and also affect atrial refractory periods to provide a substrate for the conversion of PV firing into sustained AF.\(^3-5\) More specifically, increased vagal tone has been shown to be a trigger for AF in a subset of patients.\(^6\) Enhanced vagal tone can increase the inducibility of AF,\(^7\) and elimination of vagal inputs has been shown to prevent AF recurrence in both animal models and patients with vagal AF.\(^8,9\)

Radiofrequency ablation has emerged as an effective therapy for patients with symptomatic AF. Traditionally, ablation has been used to eliminate all of the triggers for AF by isolating the PVs.\(^10\) Recent data have suggested that identification and ablation of autonomic GP during PV isolation (PVI) may improve its long-term success.\(^11-13\) However, it is unknown whether these regions can be modified during standard PV antrum isolation. Thus, the purpose of this study was to assess the effect of standard PV antrum isolation on vagal responses.

**METHODS**

**Study population:** Seventeen patients with symptomatic, drug-refractory (≥ 2 drugs) paroxysmal AF (12 men and 5 women; mean age, 60 ± 10 years, range, 41-75 years) and 4 patients with persistent AF (4 men; mean age, 66.0 ± 0.5 years, range, 66-67 years) lasting more than 1 week were enrolled in the study. All 21 patients were scheduled to undergo first-time PVI. Antiarrhythmic drugs, with the exception of amiodarone, were discontinued for 5 half-lives before PVI. Amiodarone was discontinued for 2 months before PVI. Patients were treated with the anticoagulant warfarin for at least 3 weeks with a target international normalized ratio of 1.7-2.3, and transesophageal echocardiography was performed in all the patients 1 day before PVI. Patients with any of the following conditions were excluded from the procedure: myocardial infarction during the previous 6 months, left atrial thrombus identified by transesophageal echocardiography, and implantation of a defibrillator or pacemaker. All patients provided written informed consent, and the study was approved by the Committee for Human Subject Research at our institution.

**Study 1:** Eight of the 21 patients were included in study 1. Only patients with paroxysmal (4 men and 2 women, mean age, 59 ± 11 years, range, 41-75 years) or persistent (2 men, mean age, 66 ± 0.5 years, range, 66-67 years) AF were included. The AF was refractory to at least 2 antiarrhythmic medications. Patients who had undergone open-heart surgery or who had permanent AF were excluded.
All patients gave written informed consent before the stimulation and ablation procedure.

**High-frequency stimulation and autonomic response:** Two or 3 long sheaths (SL0 and SL1, or SL0, SL0, and SL1, Daig Corp., Minnetonka, MN, USA) were introduced into the left atrium (LA) through a single transseptal puncture site by the Brockenbrough technique. After transseptal puncture, heparin was administered intravenously to maintain the activated clotting time at > 250 seconds. Right and left pulmonary angiograms obtained during the levophase of the PVs were performed to evaluate the morphology of the right and left PVs before the ablation procedure. A high-density duodecapolar circular catheter (Lasso, Biosense-Webster, Diamond Bar, CA, USA) was positioned, via a transseptal sheath, on the antrum proximal to each PV ostium. Under light general anesthesia by an intravenous administration of midazolam and fentanyl, electrical stimulation (20 Hz, 0.1-ms pulses at 15-20 volts) was applied to each of the Lasso electrode pairs (1-2 to 19-20) during spontaneous or induced AF by means of a Grass S88 stimulator with an SIU 5 stimulus isolation unit (Grass Technologies, West Warwick, RI, USA). Vagal response was defined as prolongation of the RR interval by ≥ 20%.14)

**Study 2:** Twenty-one patients including the 8 patients enrolled in study 1 were included in study 2.

**PV antrum isolation procedure:**

**Individual PV antrum isolation.** Segmental isolation of the antrum of each of the 4 PVs was performed in the first 5 patients. A PVI technique described previously was used.10) In brief, a circumferential duodecapolar catheter and a 4- or 8-mm tip steerable catheter (EP Technologies, Inc., Mountain View, CA, USA) were placed at the PV antrum through an SL0 or SL1 sheath for mapping and ablation of the antrum of each PV. Radiofrequency catheter ablation (RFCA) to isolate each PV antrum was performed under the guidance of PV circumferential mapping around the PV antrum. The catheter tip temperature was limited to 50°C at a maximum power of 30-35 W. The duration of each energy application was set to 60 seconds. The endpoint of the ablation procedure was complete bidirectional block between the 4 PVs and the LA, and the following criteria were used to confirm bidirectional PV antrum isolation: absence of PV potentials inside the PV antrum during sinus rhythm and distal coronary sinus pacing, and absence of PV to LA conduction during pacing from at least 4 points inside the PV antrum.

**Extensive ipsilateral PVI.** Extensive ipsilateral PVI was performed in the remaining 16 patients. Two duodecapolar or decapolar Lasso catheters were placed at the antra of the ipsilateral PVs.15) Linear catheter ablation of the left-sided PVs was performed at the posterior wall at least 1 cm outside the PV ostia on the basis of 2 Lasso catheters and the angiographic image. The linear ablation...
line was created from the roof of the LA to the floor of the inferior PV ostium. RFCA to the anterior wall was then performed targeting the earliest activation site recorded from the 2 Lasso catheters placed around the left-sided PVs during pacing from the distal coronary sinus. The right-sided PVs were also isolated via the same ablation process. An 8-mm tip catheter (EP Technologies, Inc.) was used, and the catheter tip temperature was set to 50-55°C at a maximum power of 30-35 W. The duration of each energy application was set to 60 seconds. The endpoint of the ablation procedure was the same as that for individual PVI.

Follow-up: After PVI, each patient was treated with warfarin for at least 6 months. Antiarrhythmic drugs were withheld after PVI in all patients with paroxysmal or persistent AF. Surface 12-lead ECG recording and 24-hour Holter monitoring were performed 1 day, and 3, 6, and 12 months after PVI. Recurrent AF was defined as AF that recurred 3 months or more after PVI. Recurrent AF was based on follow-up surface 12-lead ECG recordings, ambulatory event ECG recordings, or 24-hour Holter recordings. All patients were followed-up for at least 6 months after PVI. The mean follow-up period was 8 months (range, 6-9.5 months).

Statistical analysis: Data are expressed as the mean ± SD. Statistical analysis was performed by StatView 5.0 software (SAS Institute Inc. Raleigh, NC, USA). Between-group differences were analyzed using the unpaired Student's *t*-test. Differences in nominal data were analyzed by the *χ*² test. A *P* value < 0.05 was considered significant.

**RESULTS**

High-frequency stimulation and autonomic response: Localization of autonomic ganglia at the antra of the PVs was achieved by endocardial high-frequency stimulation through the Lasso catheter in 6 patients at the superior portion of the left superior PV (LSPV) antrum (Figures 1 and 2) and in 2 patients at the inferior portion; in 1 patient at the superior portion of the left inferior PV (LIPV) antrum and in 2 patients at the inferior portion; in 1 patient at the septal portion of the right superior PV (RSPV) antrum; and in 3 patients at the inferior portion of the right inferior PV (RIPV) antrum. A typical positive vagal response is depicted in Figure 3.

Catheter ablation: In all 5 patients with individual PV antrum isolation and all 16 patients with extensive ipsilateral PVI, 4 PVs were successfully isolated.

A decrease in sinus rate of ≥ 20% was seen in 4 patients during LSPV roof ablation, in 2 patients during RSPV septal site ablation, and in 1 patient during
Case 1

Figure 1. Response to high-frequency stimulation in case 1. The mean RR interval increased 43% with high-frequency stimulation in the superior region of the left superior pulmonary vein (LSPV).

Figure 2. Location of the high-frequency stimulation site (□) in case 1. Note that the site is in the superior region of the left superior pulmonary vein (LSPV). HIS indicates His bundle electrogram recording site; CS, coronary sinus; and Abl, ablation catheter.
RIPV bottom ablation. Second- and/or third-degree atrioventricular block (Figure 4) during sinus rhythm or a pause of more than 5 seconds during AF (Figure 5) was seen in 5 patients during LSPV roof ablation without specifically targeting

Figure 3. Stimulation sites from the lasso catheter where high-frequency stimulation decreased mean RR intervals ≥ 20%. LSPV indicates left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava; and LA, left atrium.

Figure 4. Application of radiofrequency energy at left superior pulmonary vein (LSPV) in case 4 during sinus rhythm. Note that LSPV ablation resulted in transient complete atrioventricular block (CAVB). RF indicates radiofrequency; CS, coronary sinus; and PV, pulmonary vein.
these sites. During the mean follow-up period of 8 months, recurrence of AF was documented in 5 (24%) of the 16 patients in whom atrioventricular block or a pause of > 5 seconds did not develop, whereas recurrence of AF was not documented in the 5 patients in whom atrioventricular block or a pause of > 5 seconds developed.

**DISCUSSION**

**Major findings:** This study showed that in patients undergoing a first-time PV antrum isolation procedure, vagal response can be induced by autonomic GP stimulation from the Lasso catheter placed at the antrum of each PV.

This study is the first to examine the feasibility and safety of stimulation of the GP from the Lasso catheter. Eight months of follow-up showed freedom from AF recurrence in 100% of patients in whom atrioventricular block or a pause of more than 5 seconds developed during PV antrum ablation compared to freedom from recurrence in 75% of patients in whom atrioventricular block or a pause of more than 5 seconds did not develop during PV antrum ablation.

**Localizing GP sites for ablation:** Previous studies have shown the feasibility of
cardiac GP stimulation by evoking a vagal response using high-frequency stimulation from a steerable ablation catheter.\textsuperscript{11-13,16-18} Vagal response sites are usually located at least 1-2 cm outside the PV ostia. The anterior right GP is located anterior to the RSPV; the inferior right GP is located inferior to the LIPV; the inferior left GP is located inferior to the LIPV, and the superior left GP is located superior to the LSPV. The findings of these studies were consistent with the anatomical findings reported by Armour, \textit{et al.}\textsuperscript{1} Our findings are consistent with previous reports that a vagal response was induced by high-frequency stimulation from the upper part of the superior PVs and lower part of the inferior PVs. In our study, the Lasso catheter seemed to be closer to the PV orifices than in previous studies,\textsuperscript{11-13,16-18} however, Tan, \textit{et al}\textsuperscript{19} and Matsuyama, \textit{et al}\textsuperscript{20} reported that autonomic nerves were located within 5 mm of each PV-left atrial junction. A vagal response was also noted during catheter ablation at the similar part of the PVs at which high-frequency stimulation evoked the vagal response.

\textbf{Relation of GP ablation to outcome:} Catheter ablation of GP has been shown to prevent vagal AF in canine models.\textsuperscript{8,11,21} In recent clinical studies, vagal denervation was induced by targeted GP ablation\textsuperscript{9,11,13,17} or inadvertently by standard circumferential or segmental PVI.\textsuperscript{16,22} However, only limited data have been available on the long-term benefit of vagal denervation. Pappone, \textit{et al}\textsuperscript{22} assessed the incremental benefit of vagal denervation in 297 patients undergoing circumferential pulmonary ablation for paroxysmal AF. Notably, they reported that only 1 of the 102 patients in whom vagal denervation was successful experienced recurrent AF within the following year.\textsuperscript{22} More recently, Nakagawa, \textit{et al} reported a favorable outcome for segmental PV ablation combined with vagal denervation in a series of 47 patients with paroxysmal AF and 25 patients with persistent AF. They also reported that more than 80\% of patients were free of symptomatic AF during the 1-year follow-up period after the single ablation procedure.\textsuperscript{23}

\textbf{Clinical implications:} It may be advantageous to look for vagal response sites by high-frequency stimulation from a Lasso catheter to ablate GP, and to achieve vagal denervation in addition to PV antrum ablation to avoid recurrence of AF.

\textbf{Study limitations:} Only a small number of patients with either paroxysmal or persistent AF were enrolled in this study. Furthermore, different PVI techniques were used. Thus, no statistical significance was observed in the recurrence of AF between patients with and without vagal response during ablation. Bauer, \textit{et al}\textsuperscript{16} showed that both circumferential and segmental PV ablation induce an immediate decrease in autonomic function. However, this decrease is only transient with segmental PV ablation, but it persists for at least 1 year with circumferential PV ablation.\textsuperscript{16} Verma, \textit{et al}\textsuperscript{17} reported that standard PV antrum isolation eliminates vagal responses induced by GP stimulation. Responses were not seen in any of
the 20 patients undergoing repeat PV antrum isolation, despite clinical recurrence of AF in 19 of the 20 patients at 4 ± 2 months after the initial ablation procedure. Furthermore, we did not routinely assess autonomic function after PVI by studying heart rate variability in Holter recordings. Thus, a large-scale prospective study is warranted to evaluate the efficacy of adjunctive vagal denervation during PVI to reduce the recurrence of AF.

Conclusions: GP can be identified by endocardial stimulation. The likelihood of recurrent AF is decreased when a vagal response is achieved by radiofrequency ablation.

REFERENCES


