Small or Large Isolation Areas Around the Pulmonary Veins for the Treatment of Atrial Fibrillation?
Results From a Prospective Randomized Study

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Background—Pulmonary vein (PV) isolation is a promising new treatment for atrial fibrillation (AF). We hypothesized that isolation of large areas around both ipsilateral PVs with verification of conduction block is more effective than the isolation of each individual PV.

Methods and Results—A total of 110 patients, 67 with paroxysmal AF and 43 with persistent AF, were randomly assigned to undergo either isolation of each individual PV or isolation of large areas around both ipsilateral PVs. The isolation of each individual PV was an electrophysiologically guided, ostial segmental ablation with a 64-pole basket catheter or a 20-pole circular mapping catheter (group I). Isolation of large areas was performed around the 2 ipsilateral veins with a nonfluoroscopic navigation system and a circular 20-pole mapping catheter for verification of conduction block (group II). In both groups, an irrigated-tip ablation catheter (25 to 35 W) was used to achieve complete isolation. Procedure and ablation times were longer in group II, whereas fluoroscopic time was significantly shorter (P<0.001). After a follow-up period of 15±4 months, 27 patients in group I (49%) and 37 patients in group II (67%) remained free of symptoms of AF and had no AF or atrial flutter during repetitive Holter monitoring without antiarrhythmic drug treatment after a single procedure (P≤0.05).

Conclusions—The rate of success was significantly higher and fluoroscopy times were significantly lower in the group with large isolation areas around both ipsilateral PVs than in those who underwent individual PV isolation. (Circulation. 2007;115:3057-3063.)

Key Words: arrhythmia ■ mapping ■ catheter ablation ■ fibrillation ■ tachyarrhythmias

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Previous studies identified the pulmonary veins (PVs) as the source of triggers initiating and perpetuating atrial fibrillation (AF).1-3 This new pathophysiological concept of AF entailed the development of segmental ostial isolation of each individual PV as a treatment for AF.4-7 Alternatively, circumferential anatomic ablation around the PVs without verification of conduction block was proposed as an effective treatment of AF.8,9 Two randomized studies comparing the efficacy of segmental ostial isolation with circumferential anatomic ablation showed conflicting results.10,11 Recently, Ouyang et al12,13 have shown the feasibility of complete isolation of the left atrium (LA) around both ipsilateral veins using 3-dimensional mapping and the double-Lasso technique. In contrast to circumferential anatomic ablation, the end point of this new approach is the demonstration of complete conduction block. We hypothesized that isolation of a large area around both ipsilateral PVs with verification of conduction block is more efficient in eliminating AF than isolation of each individual PV.

Methods

Patient Characteristics

In the present study, we included consecutive patients with highly symptomatic, drug-refractory paroxysmal or persistent episodes of AF. In patients with persistent AF, cardioversion was performed 6 weeks before the ablation procedure under a new antiarrhythmic drug treatment to maintain the patient in sinus rhythm. Exclusion criteria were LA diameter >55 mm, intracardiac thrombi documented by transesophageal echocardiography, myocardial infarction or cardiac surgery in the previous 3 months, and previous ablation for AF. The institutional ethics committee approved the study protocol, and written informed consent was obtained from all patients. Between December 2004 and January 2006, 110 patients were randomly assigned to undergo transseptal isolation by radiofrequency energy of each individual PV (group I) or isolation of a large area around both ipsilateral PVs (group II).
Electrophysiological Study and Ablation Procedure

Oral anticoagulation was stopped 2 days before the intervention to achieve an international normalized ratio between 1.8 and 2.0. Antiarrhythmic drug treatment was suspended for the day of the ablation procedure, restarted the following day, and stopped after 1 month. Surface electrograms and bipolar endocardial electrograms were monitored and stored on a computer-based digital amplifier/recorder system (C.R. Bard, Inc; Lowell, Mass). Vascular access was obtained through the right femoral vein, and a quadrupolar catheter (Xtreme, Sorin SPA, Milan, Italy) was positioned in the coronary sinus. After transseptal puncture, heparin was infused to maintain an activated clotting time between 250 and 350 seconds. In addition, continuous infusions with heparinized saline were connected to the transseptal sheaths to avoid clot formation or air embolism. PV ostia were localized with selective PV angiography. For segmental ostial PV ablation, a 64-pole basket catheter (Constellation, Boston Scientific, Natick, Mass) or a 20-pole circular mapping catheter with variable diameter (Optima, St Jude Medical, Inc; St Paul, Minn) was positioned in each PV. Ablation was performed with an irrigated-tip catheter (Thermo-Cool, Biosense-Webster, Inc, Diamond Bar, Calif) at the ostial position showing the earliest bipolar PV potentials. Mapping and ablation were performed during sinus rhythm for the septal veins and during coronary sinus pacing for the lateral veins.

Radiofrequency energy was applied with a maximum temperature of 50°C and power between 25 and 35 W, with an irrigation rate of 10 to 40 mL/min. The end point of ablation was PV isolation, indicated by disappearance or dissociation of the distal PV potentials as recorded with either the multipolar basket or the circular mapping catheter.

For isolation of large areas around both ipsilateral PVs, the 3-dimensional geometry of the LA was reconstructed with the EnSite NavX system (NavX; St Jude Medical). The function of the 3-dimensional mapping system has been described in detail previously. The system allows navigation inside the reconstructed chamber and a simultaneous side-to-side view on a 3-dimensional computed tomography or MRI scan of the LA obtained the day before the procedure (Figure 1). The PVs were reconstructed with all 20 poles of the circular mapping catheter used simultaneously to collect geometric points by NavX. The ostia of the PVs were localized as compared to the 3-dimensional computed tomography or MRI scan and to the angiogram of the PVs. The catheter electrodes (up to 64) are localized by NavX with a precision of 1 mm by impedance changes in an electronic field of 5.68 kHz alternating in the x-, y- and z-axis between patches attached to the body of the patient. Irrigated radiofrequency energy was delivered with a target temperature of 50°C and a power between 25 and 35 W. Radiofrequency energy was applied in each spot for a maximum of 45 seconds or until the maximal local electrogram amplitude decreased by ≥80%. Circumferential ablation was performed on the posterior wall >1 cm and on the anterior wall >5 mm away from the defined PV ostia; during this initial phase, the operator was only aware of the electrograms from the ablation and coronary sinus catheter and not from the circumferential mapping catheter. When PV conduction was still present after circumferential ablation around both ipsilateral veins, both PVs were mapped sequentially by the circular mapping catheter to localize the earliest PV potentials (Figure 2). To place the catheter as close as possible to the ablation line, the diameter of the circumferential mapping catheter was adjusted to the diameter of the PV antrum. Near the earliest PV potentials recorded by the circular mapping catheter, mapping was performed on the circumferential line with the ablation catheter guided by the 3-dimensional mapping system. If local potentials were found, radiofrequency energy was reapplied to close the conduction gap. The end point of ablation was the absence or dissociation of potentials in the isolated area as documented with the circular mapping catheter.

Postablation Care and Follow-Up

After the procedure, warfarin was restarted and intravenous heparin was administered until the international normalized ratio was ≥2. Warfarin was continued for at least 3 months. On the first postprocedural day, patients underwent surface ECG, transthoracic echocardiography, and 24-hour Holter monitoring. Antiarrhythmic drugs were stopped 1 month after the ablation procedure. One and 3 months after the procedure, the patients were seen by the referring cardiologist for 24-hour Holter monitoring. Six months after the procedure, Holter monitoring, exercise testing, and multislice computed tomography or MRI of the PVs were performed during a follow-up visit at our center. Patients with symptoms of AF but no documentation on ECG or Holter monitoring were provided with an event monitor for 8 weeks. A second ablation procedure, with the use of the same technique as the first ablation, was proposed to all patients with symptomatic recurrence of AF or atrial tachycardia (AT). A final reevaluation of symptoms and 24-hour Holter monitoring was performed 15 ± 4 months after the procedure.

Study End Points

The primary end point of the study was freedom from AF without antiarrhythmic drug treatment, indicated by absence of symptoms.
related to AF or AT, and absence of atrial tachyarrhythmias of >30 seconds’ duration on repetitive Holter monitoring after 1 ablation procedure. Because early recurrences of AF or AT within the first month after ablation may be a transient phenomenon, this time interval was excluded from analysis. The secondary end point was a combined safety end point that included pericardial tamponade, thromboembolic complications, and pulmonary vein stenosis with ≥30% loss of lumen.

Statistical Analysis
On the basis of previous studies4–6 and our own experience,7 we estimated a success rate for segmental ostial PV isolation of 65%. For isolation of a large area around the PVs with verification of conduction block, success rates of 90% have been reported.12,13 All of these studies included repeat procedures to achieve such success rates. We designed the present study to have a power of 90% to detect a difference between the 2 treatment modalities at a probability value of 0.05. This yielded a sample size of 55 patients for each group.

Continuous variables were expressed as the mean±SD and were compared by the Student t test. Categorical variables were compared by χ² analysis or with the Fisher exact test. Freedom from recurrent AF was determined by Kaplan-Meier analysis with the log-rank test. Statistical significance was reached at a P level ≤0.05.
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Patient Characteristics**

The clinical characteristics of patients in both groups are shown in Table 1. Despite the previous use of a mean of $3.2 \pm 1.1$ antiarrhythmic drugs, 67 patients had paroxysmal AF, and 43 had persistent AF. AF had first been diagnosed $5.5 \pm 2.8$ years before the patients were referred to our center for ablation. On admission to the hospital, the patients were treated as follows: class I drugs, $n = 60$; amiodarone, $n = 29$; sotalol, $n = 15$; and no antiarrhythmic treatment, $n = 6$.

**Procedural Characteristics**

The procedure time was $229 \pm 66$ minutes in group I (isolation of each individual PV) and $260 \pm 57$ minutes in group II (isolation of a large area; $P \leq 0.01$), which included a waiting period of 30 minutes after successful isolation and remapping of all PVs with the circular mapping catheter to confirm conduction block. Mean fluoroscopy time was $53 \pm 18$ minutes in group I and $40 \pm 12$ minutes in group II ($P \leq 0.001$). Total ablation time was $2963 \pm 927$ seconds in group I and $3473 \pm 1035$ seconds in group II ($P \leq 0.05$). Anatomic circumferential ablation around both ipsilateral veins with the operator blinded to the electrograms provided by the circular mapping catheter resulted in conduction block in 49% of septal veins and in only 24% of lateral veins ($P \leq 0.01$). The conduction gap for the lateral veins in 88% of cases was localized on the ridge between the anterior aspect of the PV and the LA appendage, a position at which it is difficult to stabilize the ablation catheter. In these situations, ablation was performed within 5 mm of the ostium of the PVs with a reduced power of 25 W to achieve conduction block.
Follow-Up
After a follow-up period of 15±4 months, 27 patients in group I (49%) and 37 patients in group II (67%) remained free of symptoms of AF or AT and had no tachyarrhythmias during repetitive Holter monitoring or during exercise testing after the index ablation procedure (P=0.05; Figure 3). The success rate was higher in paroxysmal AF than in persistent AF in both treatment groups, but differences did not reach statistical significance (Table 2). Five patients (2 patients in group I and 3 in group II) had no clinical symptoms of AF but had episodes of AF during Holter monitoring. Patient-activated event monitors were provided to 14 patients who complained of palpitations during follow-up but had no documentation of AF on ECG or Holter monitoring. Symptom-triggered monitoring revealed ectopic beats in 6 patients and AF in 8. AT occurred in 1 patient in group I and in 6 patients in group II, but in 4 of these 7 patients, this arrhythmia occurred only transiently during the first month after the ablation procedure (Figure 4). In 3 patients with recurrent AT in group II, a second electrophysiology study was performed. In all 3 patients, AT was related to a gap in the circumferential line, and reisolation terminated the tachycardia. In addition, in 1 patient, a focal tachycardia was evidenced after PV reisolation and successfully ablated at the LA roof.

Overall, 19 patients underwent a second ablation procedure (13 in group I and 6 in group II) for recurrent symptomatic AF during follow-up. In 16 patients, reconduction of a PV was found, and reablation was performed by repeating the initial ablation approach. In 3 patients without recurrence of PV conduction, additional linear lesions were created (roof line n=3, mitral isthmus line n=1).

Safety Analysis
In each group, 1 case of pericardial tamponade occurred and was managed by percutaneous drainage. One ostial PV stenosis of 40% was observed in each group as well (right lower PV in group I and left lower PV in group II). Neither was treated with dilation or stenting because both patients remained asymptomatic during follow-up. One patient in group II had transient generalized and pulmonary edema the day after the procedure. No thromboembolisms or fistulas between the LA and the esophageus were observed in patients in the present study.

Discussion
This is the first randomized study showing that isolation of a large circumferential area around both ipsilateral PVs with verification of conduction block is a more effective treatment of AF than isolation of each individual PV. This suggests that the atrial myocardium surrounding the PVs is involved in the pathophysiology of AF. Arrhythmogenic ostial foci,7 parasym pathetic innervation,16 and sustained rotors related to stretch17 have been observed in this area around the PVs as possible mechanisms for the initiation and perpetuation of AF.

Different methods have been described to increase the area isolated around the PVs. First, PV-antrum isolation guided by intravascular ultrasound had been proposed.18,19 More recently, Ouyang et al12,13 described a method for complete isolation of LA surrounding both ipsilateral PVs using the double-Lasso technique and the 3-dimensional mapping system Carto (Biosense-Webster). In the present study, we achieved comparable results using only 1 circumferential mapping catheter with variable diameter and the 3-dimensional mapping system NavX. The variable circumferential mapping catheter enabled the confirmation of complete isolation or, if this was not achieved, identification of conduction gaps by sequential mapping of the antrum of both
ipsilateral veins in proximity to the ablation line. Ablation for closure of gaps was guided by NavX, which visualizes the electrodes of the circular mapping catheter (Figure 2). This simplified approach reduces costs and potential complications because only 2 transseptal catheters are used instead of 3. Procedure and ablation times were significantly longer for isolation of the large areas, but on the other hand, fluoroscopy time with the 3-dimensional mapping system was significantly shorter. The most challenging ablation site for complete circumferential ablation was on the ridge between the anterior aspect of the left PVs and the LA appendage. The opportunity to navigate inside the 3-dimensional images of computed tomographic or MRI scans and/or magnetic remote control of the ablation catheter may improve the accuracy of ablation in this difficult region and may also reduce examination time.

There was no difference in complication rate between the groups. In both groups, 1 moderate asymptomatic PV stenosis and 1 case of cardiac tamponade occurred. The stenosis in group II concerned a left lower PV in which additional ostial ablations 5 mm inside the vein had been performed to achieve conduction block.

In the past, there has been extensive debate about whether complete PV isolation is necessary to cure AF.20,21 Recently, Pappone and coworkers22 have shown that completeness of lesions around the PVs is crucial for the prevention of macroreentry. In the present study, we demonstrate that mapping with a variable circular catheter is mandatory for validation of the ablation lines, because only 36% of the lines were complete after circumferential anatomic ablation. Using our approach for isolation of large areas around the PVs, only 3 patients experienced AT that required a second ablation procedure during follow-up. The creation of additional linear lesions, which may be associated with complications such as pericardial tamponade or fistula between the LA and the esophagus,23 was not necessary to achieve these results.

Study Limitations
Because 7-day Holter or daily transtelephonic recordings were not available, we only performed 24-hour Holter monitoring 1, 3, 6, and 15±4 months after the procedure. Thus, we may have missed some patients with asymptomatic AF; however, this limitation would have affected both treatment groups equally. Quantification of the ablated area might have added some information but was not available with the NavX system.

Conclusions
Isolation of a large area around the PVs is more effective in treating AF than isolation of each individual PV. It can be achieved with the use of a 3-dimensional mapping system and a single circumferential mapping catheter at a reduced fluoroscopy time. We therefore propose isolation of a large area around both ipsilateral PVs with verification of conduction block as a standard procedure for the treatment of paroxysmal and persistent AF.

Disclosures
None.

References

Figure 4. Flow chart of follow-up.

CLINICAL PERSPECTIVE
Although the pulmonary veins play an acknowledged key role in the initiation and perpetuation of atrial fibrillation, the best approach for ablation of paroxysmal and persistent atrial fibrillation remains controversial. Two basic interventional methods have been proposed: (1) small-area, segmental isolation by lesions created at the pulmonary vein ostia, with verification of conduction block, and (2) circumferential anatomic ablation around ipsilateral pulmonary veins without verification of conduction block. With the latter method, the completeness of lesions has been recognized as crucial for the prevention of macroreentry. Recently, the feasibility of achieving complete isolation of the left atrium around both ipsilateral pulmonary veins, guided by the use of 2 circular mapping catheters, has been shown. In our prospective and randomized study in 110 patients with paroxysmal and persistent atrial fibrillation, we demonstrate for the first time that large-area isolation versus 49% of those after small-area isolation. Large-area isolation was achieved with a 3-dimensional mapping system and a single circumferential mapping catheter with less fluoroscopy time than small-area isolation. We therefore conclude that a combination of circumferential ablation around both ipsilateral veins and the electrical end point of complete conduction block is feasible and superior to small-area, segmental pulmonary vein isolation.

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