Phased-Array Intracardiac Echocardiography Monitoring During Pulmonary Vein Isolation in Patients With Atrial Fibrillation
Impact on Outcome and Complications

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Background—The objective of this study was to assess the impact of intracardiac echocardiography (ICE) on the long-term success and complications in patients undergoing pulmonary vein isolation (PVI) for treatment of atrial fibrillation (AF).

Methods and Results—Three hundred fifteen patients underwent PVI for treatment of AF. Each patient underwent ostial isolation of all PVs using a cooled-tip ablation catheter. PVI was performed using circular mapping (CM) alone (group 1, 56 patients), CM and ICE (group 2, 107 patients), and CM and ICE with titration of radiofrequency energy based on visualization of microbubbles by ICE (group 3, 152 patients). After a mean follow-up time of 417 ± 145 days, 19.6% (11 of 56), 16.8% (18 of 107), and 9.8% (15 of 152) of patients in groups 1, 2, and 3 experienced recurrence of AF, respectively. Moreover, whereas no group 3 patient experienced severe ($>70\%$) PV stenosis, severe PV stenosis was documented in 3 (3.5%) of 56 patients in group 1 and in 2 (1.8%) of 107 patients in group 2 ($P<0.05$). No embolic events were detected in group 3 patients.

Conclusions—Intracardiac echocardiography improves the outcome of cooled-tip PVI. Power adjustment guided by direct visualization of microbubble formation reduces the risk of PV stenosis and improves long-term cure. (***Circulation***. 2003;107:2710-2716.)

Key Words: fibrillation, atrial ■ ablation ■ echocardiography

Atrial ectopic beats within the pulmonary veins (PVs) are responsible for initiation of atrial fibrillation (AF) in most patients.[1,2] Different approaches have been developed to electrically confine PV triggers incorporating longitudinal mapping, 3-dimensional mapping systems, empirical anatomical isolation of the PV ostia, and circular mapping–guided ostial isolation.[1–6]

Phased-array intracardiac echocardiography has been shown to be helpful in defining right and left atrial structures.[7] In interventional electrophysiology procedures, effective ablation of cardiac tissue is dependent on the extent of contact between the ablation catheter tip and the endocardial surface.[8]

We hypothesized that intracardiac echocardiography would improve long-term success rates and minimize complications associated with PV isolation procedures by allowing real-time monitoring of both PV ostium and radiofrequency (RF) energy delivery. The purpose of this study was to compare the efficacy and safety of PV isolation using circular mapping alone versus circular mapping with intracardiac echo (ICE) in patients with AF and to assess the

utility of ICE-detected microbubbles as a guide to RF titration.

Methods

Patients
Between December 2000 and May 2002, 315 consecutive patients were referred to our laboratories for ablation of AF. All patients signed a written informed consent approved by the institutional ethics committee. Antiarrhythmic drugs were discontinued at least 5 half-lives before the ablation procedure. Immediately before the procedure, transesophageal echocardiography was performed in all study patients.

Paroxysmal AF was defined as self-terminating episodes lasting ≤ 7 days. Persistent AF was considered when AF episodes lasted longer than 7 days and when pharmacological or DC cardioversion was needed to restore sinus rhythm. AF episodes failing cardioversion were classified as permanent AF.[9]

Circular Mapping–Guided PV Isolation
In group 1 (56 patients), the previously described mapping and ablation approach was used.[6,10] Pulmonary vein ostia were localized by performing PV angiography during adenosine-induced (range, 12 to 24 mg) asystole. The PV angiogram was obtained in 30-degree left
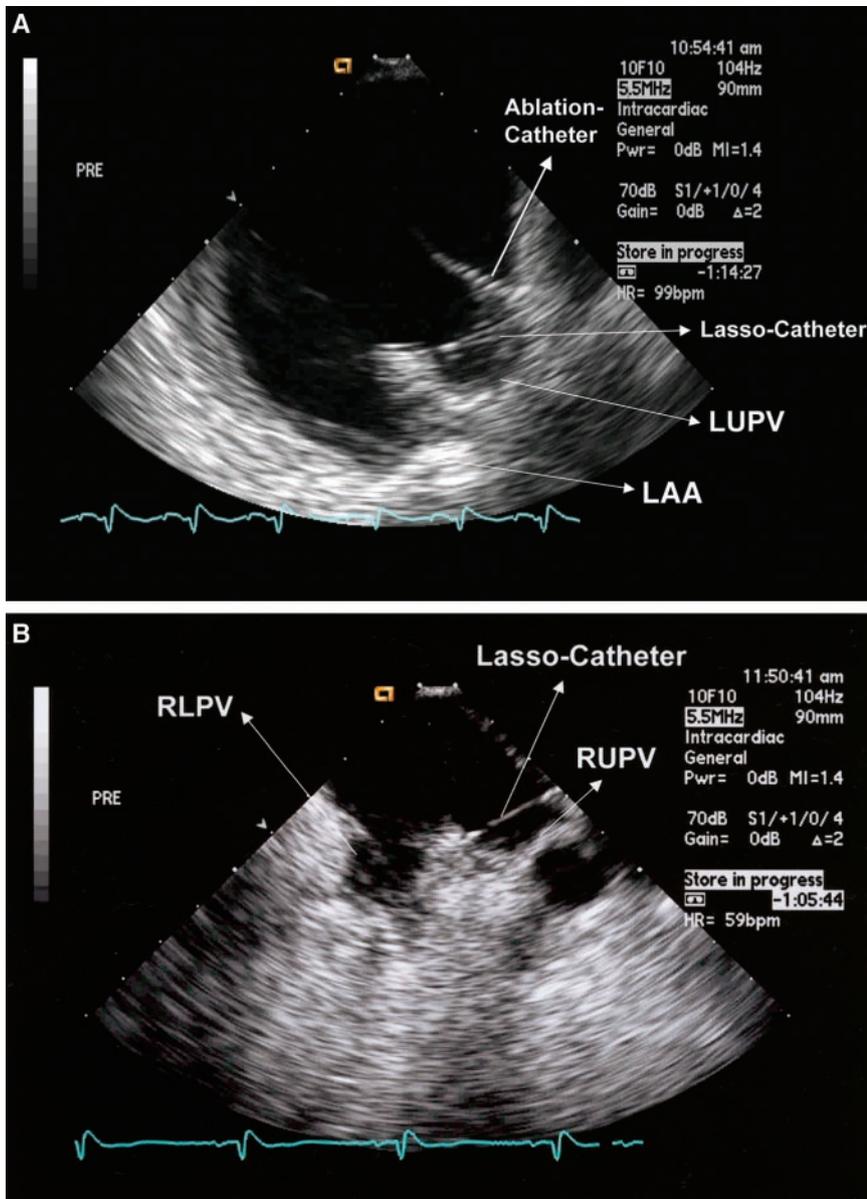
Figure 1. A, Circular mapping catheter positioned at the ostium of the left upper pulmonary vein (LUPV). LAA indicates left atrial appendage. B, Right upper and right lower pulmonary veins (RUPV and RLPV) are visible. The circular mapping catheter (Lasso-Catheter) is placed in the RUPV.

anterior oblique and 30-degree right anterior oblique views. Twenty to 25 mL of manually injected contrast was used for each angiogram. In addition, electrical mapping of PV and left atrial potentials was used to target proximal lesions. In this respect, any PV-like potentials recorded proximally to the tube-like portion of the PV as localized by angiography were considered extensions of the PV sleeves and targeted for ablation. A 4-mm cooled-tip electrode catheter (EP Technologies) was used for ablation in all study patients. A 35°C target temperature was chosen for RF energy delivery through the cooled-tip catheter. At each site energy was delivered for 45 seconds.

Intracardiac Echocardiogram and Circular Mapping–Guided PV Isolation

In group 2 patients (107 patients), intracardiac echocardiogram (ICE)-guided mapping and ablation of the PV ostia were performed using a 10-Fr 64 element phased-array ultrasound imaging catheter (AcuNav, Acuson) introduced through an 11-Fr sheath via the left femoral vein additional to a decapolar Lasso catheter (Biosense). The ICE catheter with quadrodirectional tip delectability was introduced and fluoroscopically guided to the right atrium. The ICE catheter was connected to an ultrasound platform (Acuson). The electrophysiologist performing the mapping and ablation procedure optimized the ICE images. All PV ostia were defined before transseptal puncture. Pulsed-wave doppler flow velocities of all PVs were determined before and after ablation to assess PV narrowing, and ablation at the PV ostium was aborted when the PV diastolic flow velocity exceeded 1.5 m/sec. The transseptal puncture was performed under ICE guidance to visualize the intra-atrial septum. In group 2 patients, RF energy was delivered using the cooled-tip ablation catheter (EP Technologies) applying the ablation protocol described above for group 1 patients.

Microbubbles Monitoring With Intracardiac Echocardiogram and Circular Mapping–Guided PV Isolation

In the 152 patients in group 3, ICE was used not only to ensure circular mapping catheter positioning (Figure 1) and appropriate site of energy delivery but also to guide energy titration by monitoring microbubble formation.[11–13] Two types of bubble patterns were seen with ICE: (1) scattered microbubble (type 1), reflecting early tissue overheating (Figure 2); and (2) brisk shower of dense microbubbles (type 2), reflecting impending impedance rise (Figure 3). Although we applied the same energy delivery protocol for group 1 and 2 patients, in group 3 patients power was titrated upward (5-watt
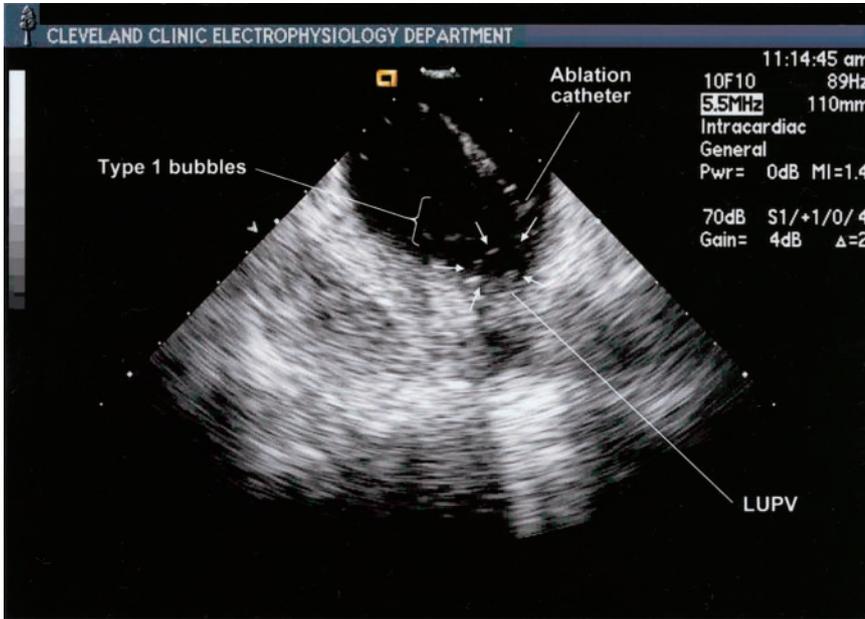
Figure 2. Localized microbubbles (type 1 bubbles) during ablation at the ostium of the left upper PV. The Lasso catheter (arrows) is placed at the ostium of the left upper pulmonary vein (LUPV).

increments), watching for formation of type 1 bubbles. When the type 1 microbubble pattern was seen, energy was titrated down by 5-watt decrements until microbubble generation subsided. Energy delivery was terminated when type 2 bubbles were seen. An attempt was made to avoid type 2 bubble formation.

Definition of Successful PV Isolation
PV isolation was considered acutely successful after abolition of all ostial PV potentials recorded on the circular mapping catheter during sinus rhythm or coronary sinus and right atrial pacing.

Follow-Up
Patients were discharged home the day after ablation day. All patients were discharged on oral anticoagulation with warfarin. Follow-up was scheduled at 1, 3, 6, and 12 months after ablation. An event recorder was given to all patients for the first month after PV isolation and repeated at the third month after ablation. After 3 months, anticoagulation was stopped unless patients experienced recurrence of AF, if more than 60% narrowing of the treated PV was

demonstrated by spiral computerized tomography performed 3 months after ablation, or if other thromboembolic risk factors were present. Patients were also monitored with Holter recording before discharge and at 3- and 6-month follow-up. In case of recurrence of symptoms, event recorder monitoring was also repeated. The occurrence of AF during the first 8 weeks after ablation was not considered a true recurrence unless it persisted beyond this time frame. For analysis, recurrence of AF was defined as AF occurring 8 or more weeks after the procedure.

Statistical Analysis
Continuous variables are expressed as mean±SD. Continuous variables were compared by Student's t test. Differences among groups of continuous variables were determined by ANOVA. Categorical variables were compared by χ^2 analysis or with Fisher's exact test. A Cox multivariate regression analysis was performed to determine the clinical predictors of freedom from AF. A Kaplan-Meier analysis with the log-rank test was used to determine the probability of freedom from recurrent AF. The Kaplan-Meier curves presented in
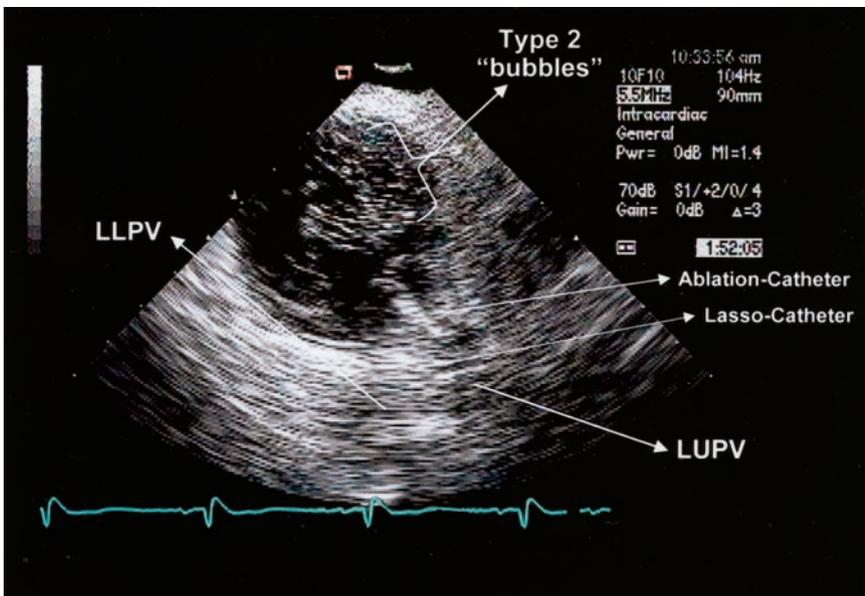
Figure 3. Shower of dense microbubbles extending to the left atrial cavity (type 2 bubbles) observed during radiofrequency delivery at the ostium of the left upper pulmonary vein (LUPV). LLPV indicates left lower pulmonary vein.

TABLE 1.   Patient Demographics

	No ICE, Group 1	ICE Without Bubbles, Group 2	ICE With Bubbles, Group 3
No. patients (male/female)	56 (43/13)	107 (85/22)	152 (117/35)
Age, y	56±9	53±11	55±12
Duration of AF, y	5.2±2.2	5.9±3.9	6.3±5.5
Paroxysmal AF	48% (27 of 56)	51% (55 of 107)	51% (78 of 152)
Persistent AF	14% (8 of 56)	9% (10 of 107)	15% (23 of 152)
Permanent AF	38% (21 of 56)	40% (42 of 107)	34% (51 of 152)
LA size, cm	4.2±0.5	4.3±0.4	4.2±0.5
SHD	34% (19 of 56)	20% (22 of 107)	22% (33 of 152)

LA indicates left atrium; SHD, structural heart disease.

this study ignore the blanking period of 60 days after the PV isolation procedure. Results with $P<0.05$ were considered statistically significant.

Results

Three hundred fifteen consecutive patients (70 women; mean age 54±11 years) with symptomatic paroxysmal (160 patients), persistent (41 patients), and permanent (114 patients) AF (mean duration, 6±3.6 years) presented for ablation of AF to our laboratory. Structural heart disease was present in 23.5% of patients (74 of 315). The demographics of the study population are given in Table 1.

Pulmonary Vein Isolation
A total of 1202 PVs in 315 patients were mapped and successfully isolated. A common PV ostium was found in 8.5% of the right PVs (26 of 315) and in 10.5% of the left PVs (32 of 315). Table 2 reveals acute and chronic results in the 3 study groups. A mean of 8.5±2 RF lesions (6.2±1.5 minutes) per PV were delivered to achieve complete isolation

in group 3 patients, whereas 14±2 (10.5±4 minutes) and 10±3 (7.5±2.2 minutes) lesions were delivered in groups 1 and 2, respectively ($P<0.05$). Fluoroscopy and procedure times were lower in group 2 (60±20 and 190±48 minutes, respectively) and 3 (59±21 and 185±65 minutes, respectively) compared with group 1 (81±29 and 250±66 minutes; $P<0.05$). In group 2 patients, we assessed the correlation between PV ostium defined angiographically and under ICE guidance in 125 PVs. The PV ostium defined angiographically was found to correlate with the ICE-defined PV ostium in only 19 (15%) of 125 PVs. In 106 (85%) of these 125 PVs isolated in group 2, ICE showed that placement of the circular catheter based on angiography was inaccurate and distal to the true PV-left atrial ostium (5±3 mm within the PV).

ICE-Guided Ablation Monitoring
Type 1 bubbles were observed during 55% of the lesions delivered in group 2 patients and during 98% of lesions delivered in group 3 patients ($P=0.009$). The correlation

TABLE 2.   Pulmonary Vein Isolation and Follow-Up Results

	No ICE, Group 1 (n=56)	ICE Without Bubbles, Group 2 (n=107)	ICE With Bubbles, Group 3 (n=152)
No. isolated PVs, RUPV/RLPV/LUPV/LLPV	56/50/56/49	107/97/107/94	152/142/152/140
AAD	3±0.7	3.6±1.1	2.6±1.3
Fluoroscopy time, min	81±29	60±20*	59±21*
Procedure time, min	250±66	190±48*	185±65*
Mean No. RF lesions/PV (min)	14±2 (10.5±4)	10±3 (7.5±2.2)	8.5±2 (6.2±1.5)*
Follow-up, days	639±79	437±46	288±67
Recurrence of AF	19.6% (11 of 56)	16.8% (18 of 107)	9.8% (15 of 152)†
Moderate PV stenosis/PV	5% (11 of 211)	4.5% (18 of 405)	2.5% (12 of 586)
Moderate PV stenosis/patient	9% (5 of 56)	6.5% (7 of 107)	4% (5 of 152)‡
Severe PV stenosis/PV	3% (6 of 211)	1% (4 of 405)	None‡
Severe PV stenosis/patient	3.5% (3 of 56)	1.8% (2 of 107)	None‡
Embolic events including TIA§	3.5% (2 of 56)	3% (3 of 107)	None‡

ICE indicates intracardiac echo; PV, pulmonary veins; RUPV, right upper pulmonary vein; RLPV, right lower pulmonary vein; LUPV, left upper pulmonary vein; LLPV, left lower pulmonary vein; LA, left atrium; and AAD, antiarrhythmic drug.

*$P<0.05$ vs group 1 applying ANOVA; †$P=0.009$ vs group 1 applying Cox regression analysis; ‡$P<0.05$ vs group 1 applying Fisher's exact test; and §1 patient in group 1 and 2 patients in group 2 experienced transient ischemic attack (TIA).

coefficient between type 1 bubble formation and maximum delivered temperature, maximum delivered power, and maximum impedance was 0.3, 0.2, and 0.4, respectively.

Type 2 bubbles were observed during 38% of lesions delivered in group 2 patients and 2% of lesions delivered in group 3 patients ($P<0.001$). Type 2 bubbles preceded impedance rise by a mean of 3.4 seconds (range, 3 to 5) and was always followed by a rise in impedance unless the power was turned off. Although impedance rise during energy delivery in group 3 lesions was negligible (0.9%), impedance rise leading to automatic termination of power delivery was observed in 21% of group 1 and 15% of group 2 lesions ($P=0.001$). The correlation coefficient between the maximum delivered temperature, maximum delivered power, maximum impedance, and the same parameters with type 2 bubbles formation were 0.4, 0.3, and 0.3, respectively. Distribution of type 1 and type 2 micro-bubbles over temperature and power ranges are shown in Figure 4.

Recurrence and Complications

Table 2 demonstrates long-term follow-up results in the 3 study groups. After a mean follow-up time of 417 ± 145 days, 14% of study patients (44 of 315) experienced recurrence of AF. Using the Cox multivariate analysis, the recurrence rate was significantly lower in patients undergoing ICE-guided PV isolation (groups 2 and 3) than in patients undergoing circular mapping–guided isolation alone (12.7% versus 19.6%; $P=0.01$). A significant difference in chronic success was also observed when comparing isolation guided by microbubble formation versus isolation guided by circular mapping alone (90.2% versus 80.4%; $P=0.009$). Moreover, patients in group 2 experienced a higher recurrence rate compared with group 3 patients (16.8% versus 9.8%; $P=0.08$). Figure 5 and 6 demonstrate AF-free survival curve for the 3 study groups.

Moderate (50% to 70%) PV stenosis was observed in 5% (11 of 211) of treated PVs in group 1, 4.5% (18 of 405) of the treated PVs in group 2, and 2.5% (12 of 586) of the treated PVs in group 3. Although no severe PV stenosis occurred in group 3, severe PV stenosis was documented in 3 (3.5%) of 56 patients in group 1 and in 2 (1.8%) of 107 patients in group 2 ($P<0.05$). Two patients in group 1 (3.5%) and 3 patients in group 2 (3%) experienced embolic events including strokes and transient ischemic attack, whereas no cerebrovascular events were detected in group 3 patients. Table 2 shows follow-up outcomes and complications.

Discussion

Main Findings

Our study proves that ICE-guided pulmonary vein isolation is more effective than angiography-guided circular mapping. In addition, monitoring of energy delivery using ICE additionally improved long-term success and was associated with decreased risk of complications.

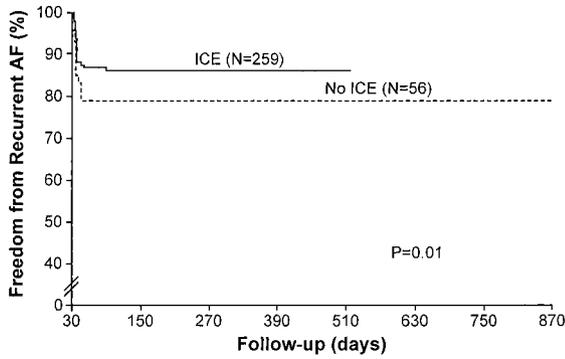### Intracardiac Echo-Guided Isolation of PV

Circular mapping–guided PV isolation for treatment of AF has been reported to be effective and feasible.[3,5,6,14] The superiority of ICE-guided PV isolation compared with
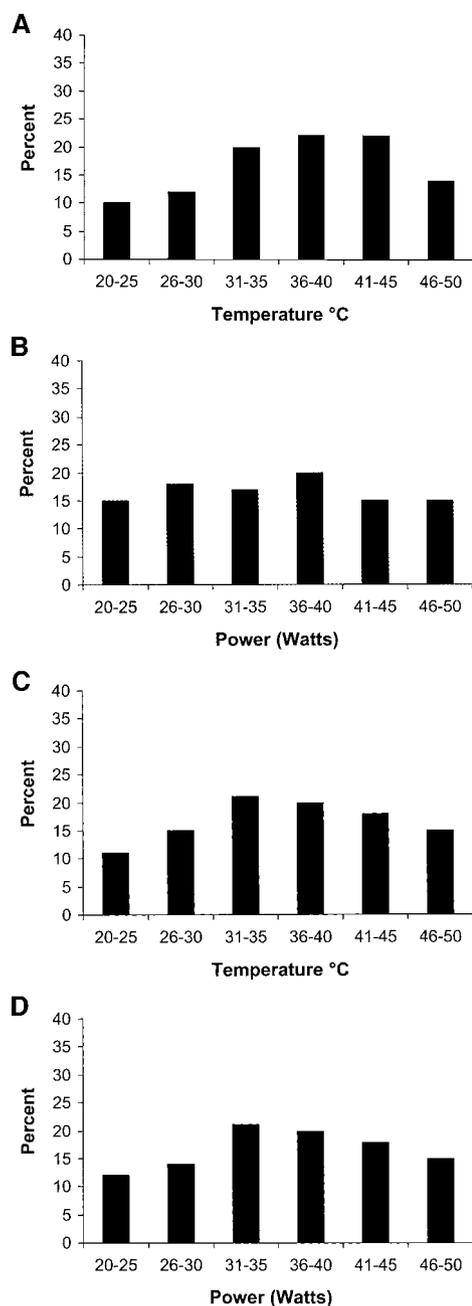
Figure 4. Distribution of lesions with type 1 bubble formation over temperature (A) and power (B) ranges, respectively. Distribution of lesions with type 2 bubble formation over temperature (C) and power (D) ranges, respectively.

angiography-guided isolation using circular mapping could be explained by 2 factors. First, from our experience it appeared that angiography-based placement of the circular mapping catheter is less accurate than ICE-assisted positioning. True ostial PV isolation requires abolition of all PV potentials that extend to the PV antrum proximal to the tube-like portion of the vein. Electrical mapping of the sleeves using the circular catheter and direct visualization of the PV ostium (Figure 1) were enhanced by ICE.

Second, poor contact between the ablation catheter tip and the endocardial surface reduces heat transfer to the tissue and allows convective heat loss into the circulating blood.[15]
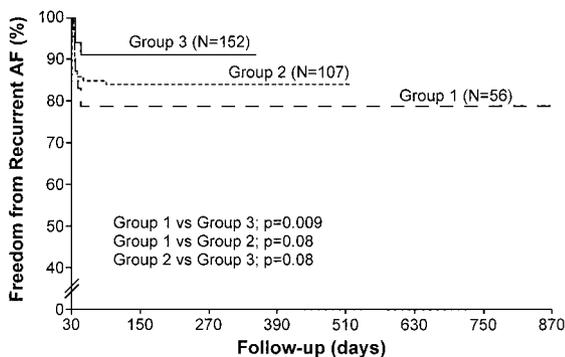
Figure 5. AF-free survival curves after PV isolation in patients ablated using the circular mapping–guided PV isolation (dashed line) and the intracardiac echo-guided PV isolation (solid line). Recurrence rate seemed to be higher using the circular mapping–guided PV isolation alone (P=0.01).

Diminished heat delivery to the PV ostial tissue may result in increased power output, inefficient lesion formation, and increased risk of coagulum format ion. Kalman et al[12] reported that less than 50% of fluoroscopically guided RF lesions were delivered with good perpendicular contact. Hence, ensuring stability and proper ablation catheter tip-tissue contact using ICE might have played an important role in the long-term cure of AF and in the chronic development of severe PV stenosis in our study patients.

Recently, Mangrum et al[16] reported their experience using radial cross-sectional intracardiac echocardiography to guide anatomically based ostial PV isolation and reported a recurrence rate of 36% after 13 ± 7 months of follow-up in patients with paroxysmal AF. In our study population, all PVs were isolated, whereas Mangrum et al isolated only PVs triggering APCs and AF during the procedure. This could explain the higher success rate in our series.

Monitoring of Energy Delivery
Radiofrequency energy is conventionally delivered using temperature, power, and impedance monitoring. Energy delivery is typically terminated after approaching programmed

Figure 6. AF-free survival curves comparing pulmonary vein isolation using the circular mapping–guided PV isolation alone (dashed line, group 1), the intracardiac echo without microbubbles monitoring circular mapping–guided PV isolation (dotted line, group 2), and intracardiac echo with microbubbles monitoring circular mapping–guided PV isolation (solid line, group 3). Recurrence rate seemed to be lower in groups 2 and 3 compared with group 1.

ablation time or after a sudden increase in impedance that suggests excessive tissue heating. Increase in impedance has been associated with increased risk of coagulum formation[15] and could be a sign of improper lesion formation,[12,13,15,17] which could create the milieu for PV stenosis. In an experimental model, Kalman et al[12] reported that showers of microbubbles and occasionally of coagulum preceded rises in impedance. These findings occurred with higher frequency when the electrode-tissue contact was suboptimal. In the present study, a poor correlation between delivered energy parameters (power and temperature) and formation of microbubbles was confirmed.

Using microbubble generation to guide energy delivery may optimize lesion formation. In addition, conventional RF energy delivery using a cooled-tip catheter is generally limited to a target temperature of 35°C. By using the ICE-guided microbubble monitoring strategy, we increased the power based on objective findings and were able to observe that bubbles are seen over a wide range of temperature varying from 20°C to 50°C.

Of interest, prevention of a dense shower of microbubbles with ICE imaging also seemed to diminish the risk of embolic events in our patient population.

In group 3, showers of dense microbubbles, which preceded impedance rise by 3 to 5 seconds in our study, were avoided and, when seen, were a reason for discontinuation of RF delivery. This may have led to less-extensive endothelial and subendothelial layers injury, explaining the lower occurrence of severe PV stenosis in group 3 patients. It is important to realize that these data may not apply to ablation with opened irrigation tips.

Study Limitations
The lack of random assignment to treatment groups could have affected our findings. However, given the similarity among the treatment groups in baseline characteristics, we feel this is unlikely. The time at which the procedures were performed differed among the groups. We had acquired the most experience in performing pulmonary vein isolation for the patients in group 3, and this increased experience may have resulted in improved technical expertise at performing circular mapping and ablation. On the other hand, the first 70 patients undergoing circular mapping–guided isolation were not included in this series. This should have limited the effect of the learning curve on the outcomes reported.

Conclusions
This is the first study that has compared ICE-guided circumferential PV isolation to circular mapping–guided PV isolation in patients with AF. ICE-guided PV isolation was more effective than conventional circular mapping–guided PV isolation in patients with AF. Moreover, during radiofrequency, energy delivery monitoring of microbubble formation using ICE improved long-term success rates and decreased complications.

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