Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, which is associated with a marked morbidity, mortality, and socioeconomic burden. Catheter ablation targeting the pulmonary veins (PVs) has been reported to be a potential method for treating AF since late 1990s. As techniques and technologies have improved, catheter ablation of AF has become a standard and effective therapy for patients with symptomatic and drug-refractory AF, and its popularity continues to escalate. Recently, 2 centers reported the long-term results of catheter ablation in AF and demonstrated that the arrhythmia-free survival rate after a single procedure was about 29% to 47% at 5 years. However, the patients enrolled in these 2 studies had mainly paroxysmal AF and accounted for 100% and 64% of the study population, respectively. Since the indications of AF ablation have broadened to include nonparoxysmal AF patients, the data on the long-term efficacy of ablation in patients with nonparoxysmal AF have become important but seem to be lacking. Therefore, the aim of the present study was to investigate the long-term outcomes of catheter ablation in patients with nonparoxysmal AF.
investigate the long-term outcome of catheter ablation in patients with nonparoxysmal AF.

**Methods**

**Study Population**

Patients with symptomatic drug-refractory nonparoxysmal AF who received radiofrequency catheter ablation for the first time under the guidance of a NavX mapping system (NavX, St Jude Medical, Inc, St. Paul, MN) from 2006 to 2008 were studied (n=103). Patients who did not receive regular follow-up for at least 1 year after the ablation were excluded (n=15). Finally, there were 88 patients enrolled in the present study. Nonparoxysmal AF included the patients with persistent and long-standing persistent AF, as defined by the consensus documents.10 The CHADS2 score was calculated for each patient by assigning 1 point each for an age >75 years, hypertension, diabetes mellitus, and heart failure and 2 points for a previous stroke or transient ischemic attack.10

**Stepwise Catheter Ablation Approach**

The stepwise procedure of the catheter ablation of AF involved the following steps:1,11,12

Step 1 (isolation of the PVs): After a successful transseptal procedure, continuous circumferential lesions were created encircling the right and left PV ostia guided by the NavX system using an irrigated 3.5-mm ablation catheter (Chilli II, EPT, Boston Scientific Corp, San Jose, CA). The intention was to place the radiofrequency lesions at least 1 to 2 cm away from the angiographically defined ostia. After completion of the circumferential lesion set, the ipsilateral superior and inferior PVs were mapped carefully by a circular catheter recording (Spiral, AF Division, St Jude Medical). Successful circumferential PV isolation was demonstrated by the absence of or dissociated PV activity during AF. After restoration to sinus rhythm by procedural termination or electric cardioversion, PV–left atrium (LA) conduction block was confirmed again. Additional applications of radiofrequency energy for the residual PV potentials were performed from the atrial side of the PV antrum, using the electrogram-guided approach to obtain entrance block.

Step 2 (linear ablation by the anatomic approach): If AF did not stop after the first step, additional linear ablation was performed at both the anterior roof and lateral mitral isthmus. Linear ablation was guided by the NavX system with the creation of split potentials (after restoration to sinus rhythm) or an electrogram voltage reduction of >50% as the end points after each application of radiofrequency energy. A right atrial cavotricuspid isthmus ablation was performed with an 8-mm tip EPT ablation catheter (Boston Scientific Corp). Bidirectional conduction block of the cavotricuspid isthmus was confirmed after restoration to sinus rhythm.

Step 3 (continuous complex fractionated atrial electrogram (CFAE) site ablation): If AF did not stop after steps 1 to 2 of the ablation procedure, an additional CFAE ablation was performed sequentially, based on the results of the CFAE maps after the circumferential PV isolation. The details about the CFAE mapping and ablation were reported in our previous publications.12,13 In brief, the CFAE ablation was confined to the continuous CFAEs, defined as an electrogram fractionation or repetitive rapid activity lasting for >8 seconds with an averaged fractionated interval of <50 ms over 5 seconds,14 in the LA and right atrium. The end point of the CFAE ablation was to obtain a prolongation of the cycle length (disappearance of continuous CFAEs), eliminate the CFAEs (thus, a fractionation interval of >120 ms, and disappearance of CFAEs), or abolish the local fractionated potentials (bipolar voltage <0.05 mV). The CFAE sites were assessed by an automatic algorithm immediately after the ablation. If the AF terminated during the linear ablation through the CFAE sites, complete linear ablation to an anatomic obstacle or nearest line was performed to prevent proarrhythmias.

Step 4 (non-PV ectopy ablation): If the AF still did not stop after the step 1 to 3 procedures, sinus rhythm was restored by electric cardioversion. After sinus rhythm was restored from AF either by procedural AF termination or electric cardioversion, mapping, and ablation were applied to spontaneously initiating focal atrial tachycardia and non-PV ectopy that initiated AF.

If the AF became organized during the step 1 to 3 procedures, electroanatomic mapping was performed and radiofrequency ablation was performed to terminate the organized tachycardia. The AF procedural termination was defined as restoration to sinus rhythm during the ablation in steps 1 to 3. AF induction was not performed in the patients with persistent and long-standing persistent AF.

**Postablation Follow-Up**

After the catheter ablation, all patients received antiarrhythmic drugs for 8 weeks to prevent any early recurrence of AF. Patients underwent regular follow-up (2 weeks after the catheter ablation, then every 1–3 months) at our cardiology clinic or with the referring physicians. During the follow-up, 24-hour Holter monitoring and/or cardiac event recording with a recording duration of 1 week were performed. The recurrence was defined as an episode of atrial arrhythmias lasting >30 seconds and confirmed by electrocardiograms 2 months after the ablation (blanking period). Freedom of recurrence was defined as the absence of atrial arrhythmias without using any antiarrhythmic agent after the catheter ablation. The long-term efficacy was assessed clinically on the basis of the clinical symptoms, resting surface 12-lead ECG, 24-hour Holter monitoring, and/or 1 week cardiac event recordings.

**Statistical Analysis**

Differences between the continuous values were assessed using an unpaired 2-tailed t test for normally distributed continuous variables, the Mann-Whitney test for skewed variables, and the χ2 test for nominal variables. The recurrence-free survival curve was plotted via the Kaplan-Meier method with the statistical significance examined by the log-rank test. A Cox regression analysis was used to identify the factors associated with first recurrence for those variables with probability values <0.1 between patients with and without recurrences. Variables selected to be tested in the multivariable analysis were those with a probability value <0.1 in the bivariate models. The optimal cutoff value of the LA dimension in the prediction of recurrence was identified using the receiver operating characteristic (ROC) curve. All statistical significances were set at a P<0.05 and all statistical analyses were carried out by SPSS 17.0 software (SPSS Inc).

**Results**

**Baseline and Procedural Characteristics**

The study consisted of 88 nonparoxysmal AF patients; 52 of them had long-standing persistent AF. AF had been persistent for 7.9±2.0 months in patients with persistent AF and 7.4±3.0 years in those with long-standing persistent AF. The mean age of the study population was 52.3±10.4 years, with 75 men. The median value (interquartile range) of the CHADS2 score was 1 (0–3).

The mean procedure and fluoroscopy times were 185.9±44.2 and 119.0±39.2 minutes, respectively. All patients received a circumferential isolation of all 4 PVs, and 77 patients (88.6%) received an LA linear ablation. Only 54 of 88 patients underwent a continuous CFAE ablation, because 10 patients achieved AF procedural termination and the other 24 patients had a disappearance of continuous CFAEs after the circumferential PV isolation. Most of CFAE areas were located at LA septum, followed by LA appendage and ridge, mitral annulus region, proximal coronary sinus, LA posterior wall, and LA roof. The total times of radiofrequency applications for PV isolation, linear, and CFAE ablations were 53.3±10.7, 18.1±8.0, and 16.8±7.2 minutes, respectively. A total of 41 non-PV triggers were present in 34 patients.
(38.6%), and all were eliminated successfully. The anatomic distributions of these non-PV triggers were as follows: 9 at LA anterior wall and LA appendage, 8 at LA septum, 5 at LA posterior wall, 4 at ligament of Marshall, 8 at coronary sinus ostium and crista terminalis, and 7 at superior vena cava. AF procedural termination occurred in 26 patients (29.5%).

Long-Term Results and Predictors of Recurrence After a Single Procedure

There were 63 patients (71.6%) with recurrences (47 patients with AF and 16 patients with atrial flutter/atrial tachycardia) after the initial procedure during a median follow-up period of 36.8 months. The mean duration from the ablation to recurrence was 7.2±6.2 months. The recurrence-free survival curve is shown in Figure 1, and around 84% (53/63) of recurrences occurred within 1 year after the catheter ablation. The baseline characteristics of the patients with and without recurrences are shown in Table 1. Patients with recurrences had a larger LA dimension compared with those without recurrences. Long-standing persistent AF, CHADS2 scores of ≥3, and the LA diameter were identified to be significant predictors of recurrences in the multivariable regression models (Table 2).

CHADS2 Score, LA Dimension, and Recurrence

In addition to the usefulness in predicting recurrences after catheter ablation, different patterns of recurrences were also noted among the patients with different CHADS2 scores. Among the 63 patients who had recurrences after the catheter ablation, all recurrences happened within 1 year after the procedure in the patients with CHADS2 scores of ≥3. On the other hand, there were 22.7% of the patients whose CHADS2 scores were <3 who had recurrences 1 year after the catheter ablation (Figure 2). Besides the CHADS2 score, the LA dimension at a cutoff value of 44 mm identified by the ROC curve also predicted recurrences significantly in the Kaplan-Meier analysis (79.2% versus 62.5%, log-rank probability value=0.042). Of the 14 patients with CHADS2 scores ≥3 and an LA dimension ≥44 mm, all had recurrences within 1 year after the procedure (Figure 3).

Long-Term Results After Multiple Procedures

A flow chart detailing the clinical outcome after multiple procedures is shown in Figure 4. The recurrence-free rate increased from 28.4% after the first procedure to 47.7% after the second procedure and 51.1% after the third procedure. Among the 41 patients (30 patients with recurrent AF and 11 patients with atrial flutter/atrial tachycardia) who received a second procedure, PV reconnections (at least 1 PV) were noted in 39 patients (95.1%). The mechanism of atrial flutter/atrial tachycardia was a conduction gap in the lateral mitral isthmus in 3 cases, a conduction gap in the roof line in 2 cases, a reentry circuit due to the gap of previous PV isolation line in 3 cases, and focal atrial tachycardia in 3 cases (1 LA septum, 1 LA posterior wall, and 1 crista terminalis). There were 6 patients who received a third procedure, and all of them (100%) had PV reconnections.
Discussion

Main Findings
In this study, we investigated the long-term results of the catheter ablation in nonparoxysmal AF patients with a median follow-up period of 3 years. The main findings were as follows:

1. The recurrence-free rate was only 28.4% after a single procedure and could increase to 47.7% after multiple procedures.
2. The combination of the LA dimension and CHADS2 score can identify patients who will have recurrences after catheter ablation.

Long-Term Results of Catheter Ablation in Nonparoxysmal AF
Several studies reported the long-term effects of catheter ablation in AF patients.6,7,15–17 Ouyang et al6 investigated 161 paroxysmal AF patients with a normal left ventricular ejection fraction who received catheter ablation from 2003 to 2004 and demonstrated that stable sinus rhythm was achieved in 46.6% of the patients after the initial procedure; 79.5% of the patients after multiple procedures during a median follow-up of more than 4 years. The recent study performed by Weerasooriya et al,7 which enrolled 64 paroxysmal, 22 persistent, and 14 long-standing persistent AF patients receiving ablation from 2001 to 2002, showed that the 5-year arrhythmia-free survival rates after a single and multiple procedures were 29% and 63%, respectively. Tzou et al15 reported the long-term outcome in 123 AF patients (104 had paroxysmal AF) who were free from AF 1 year after PV isolations from 2000 to 2003 and revealed that the late recurrence rate was around 7% per year. Recently, Wokhu et al16 analyzed the ablation outcome in 428 paroxysmal and 346 persistent AF patients and demonstrated that the cumulative recurrence rate at 30 months was 57% for persistent AF (regardless of the use of antiarrhythmic agents). Although previous studies have reported long-term outcome, most of the patients in these studies had paroxysmal AF. In addition, methods for ablation have also evolved. Despite the fact that the study performed by Wokhu et al enrolled a large number of persistent AF patients, these patients had received catheter ablation during a wide range of time (from 1999–2006), with different ablation strategies (either a PV isolation or a wide area circumferential ablation). In comparison to these previous studies, we focused on the ablation outcomes in patients receiving catheter ablations following the same strategy during a more recent and narrower period and may provide information more useful to the current practice. Furthermore, we only enrolled patients with nonparoxysmal AF, because the natural course after the ablation may differ between paroxysmal and persistent AF.

According to the current AF management guidelines, catheter ablation of drug-refractory persistent and long-standing persistent AF is a class IIa and IIb recommendation, respectively.9 Since these procedures become more widely performed and increasingly influence the overall healthcare costs, the data about the long-term effectiveness of catheter ablation in nonparoxysmal AF patients have become important. Our study pointed out that the recurrence rate after catheter ablation of nonparoxysmal AF was as high as 71.6% after a single procedure, and repeat ablations were necessary to raise the recurrence-free rate to 51.1%. Therefore, the decision to perform the ablation in nonparoxysmal AF patients should be made cautiously by the physicians in regard to the high recurrence rate; and patients should be informed about the high possibility and necessity of multiple procedures to achieve the freedom of the arrhythmia. Although the recurrence-free rate was only around 50%, sinus rhythm could be restored from persistent AF in 67 of 88 patients.

Table 2. Cox Regression Analysis for Predictors of Recurrences After a Single Procedure of AF Ablation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bivariate Analysis*</th>
<th>Multivariable Analysis†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Longstanding persistent AF</td>
<td>1.657 1.184–2.790</td>
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<tr>
<td>CHADS2 score ≥3</td>
<td>1.790 1.037–3.089</td>
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<tr>
<td>LA diameter , per mm</td>
<td>1.057 1.017–1.099</td>
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</tr>
<tr>
<td>Procedural termination</td>
<td>0.715 0.400–1.278</td>
<td>0.258</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; HR, hazard ratio; CI, confidence interval; and LA, left atrium.
*Variables with P values <0.1 in Table 1 were analyzed in the bivariate analysis.
†The multivariable analysis included variables whose P values were <0.1 in the bivariate model.

Figure 2. Different patterns of recurrences after a single procedure in patients with different CHADS2 scores. Among the 63 patients who had recurrences after catheter ablation, all recurrences happened within 1 year after the procedure for the patients with CHADS2 scores of ≥3. On the contrary, there were 22.7% of patients whose CHADS2 scores were <3 who had recurrences 1 year after the catheter ablation.
(76.1%) after multiple procedures during the long-term follow-up. Since the presence of sinus rhythm was demonstrated to be associated with a lower risk of death in the subgroup analysis of the AFFIRM trial,\textsuperscript{18} whether catheter ablation of nonparoxysmal AF can reduce further cardiovascular events deserves a large-scale, randomized trial to study this.

**CHADS\(_2\) Score and Recurrence After Catheter Ablation During Long-Term Follow-Up**

The LA dimension and a CHADS\(_2\) score of ≥3 were identified to be significant predictors of recurrences after catheter ablation in the present study. The CHADS\(_2\) score, which was initially developed for the stroke risk stratification in AF patients, was a convenient scoring system to evaluate the complexity of the comorbidities and aging process and can represent the adverse effects of systemic disease and old age on the atrium.\textsuperscript{19} A high CHADS\(_2\) score was proved to be associated with a poor outcome after catheter ablation in patients with paroxysmal AF in our previous publication.\textsuperscript{19} In the present study, we further demonstrated that it was also useful in identifying patients at risk of recurrence after ablation of nonparoxysmal AF. Patients with CHADS\(_2\) scores of ≥3 had a higher percentage of non-PV triggers compared with the patients with scores of <3 (63.6% versus 30.3%, \(P=0.005\)). We also observed a different pattern of recurrence for the patients with CHADS\(_2\) scores of ≥3 who will have recurrence within 1 year after the procedure. These findings suggested that systemic diseases play an important role in affecting the atrial substrate and determining the ablation outcomes in nonparoxysmal AF patients. Moreover, the recurrence rate was 100% at 1 year for the patients whose LA dimensions were ≥44 mm and had a CHADS\(_2\) score of ≥3. The LA diameter before the catheter ablation represents the severity of the structural remodeling of the LA due to persistent AF, and the high CHADS\(_2\) score may imply that the LA will still have damage due to the adverse effects of systemic disease after the catheter ablation.

**Figure 3.** Recurrence-free survival curves after a single procedure in the different groups of patients. The recurrence rate was 100% within 1 year in patients with a CHADS\(_2\) scores of ≥3 and an LA dimension ≥44 mm. LA indicates left atrium.

**Number at risk**

<table>
<thead>
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<th>Group 3</th>
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</table>

**Figure 4.** Flow chart of the clinical outcome after multiple procedures. The recurrence-free rate after catheter ablation was 28.4%, 47.7%, and 51.1% after the first, second, and third procedures, respectively.
Study Limitations
There were several limitations to the present study. First, the results of the current study may not be generalized because it was a single-center experience. We performed catheter ablation of nonparoxysmal AF according to the uniform rules in our laboratory, and therefore we were not able to compare the recurrence rates between the different ablation strategies. However, the strategy we used for ablation, PV isolation plus substrate modification, did comply with the current guidelines of the Heart Rhythm Society. Second, although we collected patients’ information systematically and followed up the ablation outcome prospectively according to the standard protocol in the laboratory, some detailed information about the severity of the underlying diseases, such as the glycemic control of diabetes, was not available for every patient. Third, the number of patients is relatively small. However, the number of nonparoxysmal AF patients enrolled in the present study was larger than most of the other published studies with a long-term follow-up. It provided us the information about the long-term results of catheter ablation in nonparoxysmal AF patients in the real world, and further large-scale and multicenter trials will be necessary to further investigate the issue. Last, although we tried our best to investigate the ablation outcome by following patients for a longer period, the results of the present study may still not be able to represent the true “long-term” outcome because AF is a life-long condition and could not be characterized in 3-year snapshots.

Conclusion
The long-term recurrence rate after catheter ablation of nonparoxysmal AF was as high as 71.6% after a single procedure, and multiple procedures were necessary to raise the recurrence-free rate. The catheter ablation may not be effective in eliminating nonparoxysmal AF for patients with an enlarged LA and high CHADS2 score. The results of the present study suggest that how to select the patients suitable for catheter ablation of nonparoxysmal AF was an important issue and deserves more attention.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Catheter ablation targeting the pulmonary veins has been reported to be a potential method for treating atrial fibrillation (AF) since late 1990s. As techniques and technologies have improved, the indications of AF ablation have broadened to include nonparoxysmal AF patients. Therefore, the data about the long-term efficacy of catheter ablation for nonparoxysmal AF are important but seem to be lacking. In the present study, we investigated the ablation outcome in a total of 88 nonparoxysmal AF patients with a median follow-up period of 3 years. The recurrence-free rate (without antiarrhythmic drugs) was 28.4% after a single procedure and could increase to 47.7% after multiple procedures. For patients with a CHADS2 score of ≥3 and a left atrial dimension ≥44 mm, all of them had recurrences within 1 year after the procedure. Therefore, the decision to perform the ablation in nonparoxysmal AF patients should be made cautiously by the physicians in regard to the high recurrence rate, and patients should be informed about the high possibility and necessity of multiple procedures to achieve the freedom of the arrhythmia. Despite the high recurrence rate of atrial arrhythmias, sinus rhythm could be restored from persistent AF in 67 of 88 patients (76.1%) after multiple procedures.
Clinical Outcome of Catheter Ablation in Patients With Nonparoxysmal Atrial Fibrillation: Results of 3-Year Follow-Up
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