Clinical Investigations

Atrial Electroanatomical Remodeling as a Determinant of Different Outcomes Between Two Current Ablation Strategies: Circumferential Pulmonary Vein Isolation Vs Pulmonary Vein Isolation

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ABSTRACT

Background: The purpose of this study was to investigate the relationship between the efficacy of the 2 different ablation techniques of atrial fibrillation (AF) and left atrial (LA) size.
Methods and Results: A total of 81 patients with paroxysmal AF (n = 58) or persistent AF (n = 23) refractory to antiarrhythmic drugs underwent circumferential pulmonary vein isolation (PVI; n = 45) or PVI (n = 36) without respect to echocardiographic results for LA volume index (LAVI). Of the 81 patients, 41 had less dilated LA (group 1; LAVI <27 cc/m^2) and 40 had dilated LA (group 2; LAVI ≥ 27 cc/m^2). During the 9-month follow-up, 33 patients (73.3%) after circumferential PVI and 18 (50%) after PVI ($P = .031$) were free of arrhythmia. The risk of recurrence was associated with persistent AF, hypertension, LAVI>27 ml/m^2, PVI, early recurrence of AF, and lower left ventricular (LV) ejection fraction (all P value $<.05$). In the univariate analysis of each group, PVI (hazard ratio [HR]: 2.92, 95% confidence interval [CI]: 0.12–7.08, $P = .018$) was associated with late recurrence only in group 2. Cox regression analysis also showed that PVI (HR: 5.6, 95% CI: 1.9–16.56, $P = .002$) was a significant independent predictor of recurrence only in group 2.
Conclusions: Circumferential PVI is more effective than PVI only in patients with a structural change of the atria, that is, a dilated LA. Our study suggests that a successful outcome in dilated LA may depend on wide modification of LA electroanatomical substrates, but wide ablation in less dilated LA may be unnecessary. Different technical strategies according to LA size are required for more a effective outcome.

Introduction

Arrhythmogenic foci within the pulmonary veins (PVs) often initiate and/or perpetuate atrial fibrillation (AF).[1,2] Pulmonary vein isolation (PVI) based on isolation of the arrhythmogenic PVs from the left atrium (LA) has been shown to cure AF.[2,3] However, it has recently been reported that circumferential LA ablation is more effective in eliminating AF than PVI.[4,5] The incremental efficacy of circumferential LA ablation has been suggested to be attributable to a wide reduction in the anatomical and electrical substrate, that is, atrial debulking.[6,7] On the other hand, LA enlargement is accompanied by structural remodeling associated with the substrate of AF.[8–11] It has not been established whether the atrial debulking strategy as a "wide area" ablation can be applied to patients with less dilated LA and, accordingly, relatively less substrate of AF. Furthermore, it has not yet been shown whether the different efficacy of these techniques depends on LA size. Accordingly, the purpose of this study was to investigate the relationship between the efficacy of the 2 different techniques and LA size.

Methods

Patients

A total of 81 consecutive patients with symptomatic paroxysmal or persistent AF and drug-refractory AF episodes were included in this study. Exclusion criteria were intracardiac thrombi, left ventricular (LV) ejection fraction <35%, history of myocardial infarction, or cardiac surgery in the previous 3 months. Patients had a mean age of 52 years (range 30–72). Paroxysmal AF was seen in 58 patients (71.6%) and persistent AF in 23 patients (28.4%). The mean AF duration was 5.1 years in all patients. A total of 28 patients (34.6%) had a history of hypertension and 6 (7.4%) had a history of diabetes mellitus. All patients provided informed written consent prior to the procedure. All antiarrhythmic medications were discontinued 4 to 5 half-lives prior to the procedure. Transthoracic echocardiography was performed

Received: October 22, 2008
Accepted with revision: December 2, 2008

Clin. Cardiol. 33, 3, E69–E74 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20567

before the procedure. The 81 patients were consecutively assigned to either PVI (36 patients) or circumferential PVI (45 patients) without respect to the echocardiographic results for LA volume and type of AF (paroxysmal vs persistent AF). From June 2005 to May 2006, AF patients undergoing catheter ablation were assigned to PVI and from June 2006 to May 2007, to circumferential PVI. LA volume index was measured by the prolate ellipsoid method,[12] with an index cut off level of 27 ml/m^2.[13,14] Catheter electrodes were inserted with the use of 1 or both femoral veins. The LA was accessed by double transseptal puncture or via an open fossa ovalis. A quadripolar electrode catheter (EP Technologies Inc., San Jose, CA) was positioned within the coronary sinus and used for recording and atrial pacing. Systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of ∼300 seconds after transseptal catheterization.

For PVI, a circular, steerable, decapolar mapping catheter (Lasso, Biosense Webster, Inc.) was inserted. After the PV was entered, the circular mapping catheter was positioned as close as possible to the PV ostium. Circular mapping was performed by obtaining 10 bipolar electrograms (1–2, 2–3, up to 10-1 electrode pairs) from the circularly-arranged electrodes of the mapping catheter. Each vein was mapped circumferentially to document typical sharp local PV potentials during steady state coronary sinus pacing (left PVs) or sinus rhythm (right PVs). PV isolation was performed (via a 4-mm tip ablation catheter) by applying radiofrequency current at the sites showing the earliest bipolar PV potentials during sinus or paced rhythms. Radiofrequency current was applied with the maximum temperature set at 50 °C and the power set at 30 to 35 W. PV isolation was confirmed as the absence of PV potentials in sinus rhythm, rapid atrial pacing, and/or isoproterenol infusion. Linear ablation of the cavotricuspid isthmus was created with the achievement of a bidirectional isthmus conduction block in each patient in order to prevent the occurrence of typical atrial flutter after AF ablation.

For circumferential PVI, continuous circumferential lesions were created encircling the right and left PV ostia guided by the NavX system using a 8-mm-tip ablation catheter (EP Technologies, Boston Scientific, Inc., San Jose, California). Radiofrequency current was applied with maximum temperature (55 °C) and maximum power (30 to 35 W) to encircle the left-sided and right-sided PVs. Continuous circumferential lesions were created 1 to 2 cm from the PV ostia to encircle right and left PVs. Additional lines were created in the posterior LA between the 2 encircling lesions. When there were any PV potentials within the PVs, PV isolation was performed as previously described.[15,16] The endpoint of circumferential PVI was the absence of PV potentials in sinus rhythm, RA (rapid atrial) pacing, and/or isoproterenol infusion. An additional linear ablation of the cavotricuspid isthmus was also created by the same method of PVI previously mentioned.

Patients remained hospitalized under continuous rhythm monitoring for at least 5 days after the ablation procedure. Heparin infusion was continued until the international normalized ratio was ≥2.

All patients were scheduled for visits in an outpatient clinic at 1, 2, 3, 6, and 9 months after the first ablation. At each of these visits, intensive questioning for arrhythmia-related symptoms (fatigue, dizziness, and nausea) since the last follow-up visit and 12-lead electrocardiography was performed. One-day Holter monitoring was performed whenever there were symptoms such as palpitation and dizziness, and at 3, 6, and 9 months in all patients. Early recurrence of AF (ERAF) was defined as AF occurring within 1 week. Late recurrence of AF was defined as AF occurring beyond 2 months after the procedure.

Statistic Analysis

All continuous data are reported as the mean ± SD and categorical variables are reported as proportions. Group comparisons used the Student *t* test for continuous variables and the χ^2 test with the Fisher exact test for categorical data. A Kaplan-Meier analysis with the log-rank test was used to determine the probability of freedom from late recurrence of AF. A multivariate Cox regression analysis was performed to determine the independent predictors of late

Table 1. Comparison of Clinical Characteristics Between Patients Undergoing Circumferential Pulmonary Vein Isolation Vs Pulmonary Vein Isolation

	Circumferential PVI (n = 45)	PVI (n = 36)	*P* Value
Age, years	53 ± 11	50 ± 10	.29
Sex (M), n (%)	38 (84.4)	31 (86.1)	.83
Alcohol, n (%)	14 (31.1)	11 (30.6)	.96
Hypertension, n (%)	19 (42.2)	9 (25)	.11
Diabetes, n (%)	4 (8.9)	2 (5.6)	.57
Body mass index, kg/m²	25 ± 2.7	24.8 ± 2.3	.7
Paroxysmal AF, n (%)	31 (68.9)	27 (75)	.54
Duration of AF, years	4.8 ± 5.3	5.5 ± 3.5	.52
EF, %	63 ± 7	62 ± 8	.19
LA volume index ≥27 ml/m²	25 (55.6)	15 (41.7)	.21
ERAF, n (%)	14 (31.1)	13 (36.1)	.63
Late recurrence of AF, n (%)	12 (26.7)	18 (50)	.031

Abbreviations: AF = atrial fibrillation; EF = ejection fraction; ERAF = early recurrence of atrial fibrillation; LA = left atrial; PVI = pulmonary vein isolation.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20567

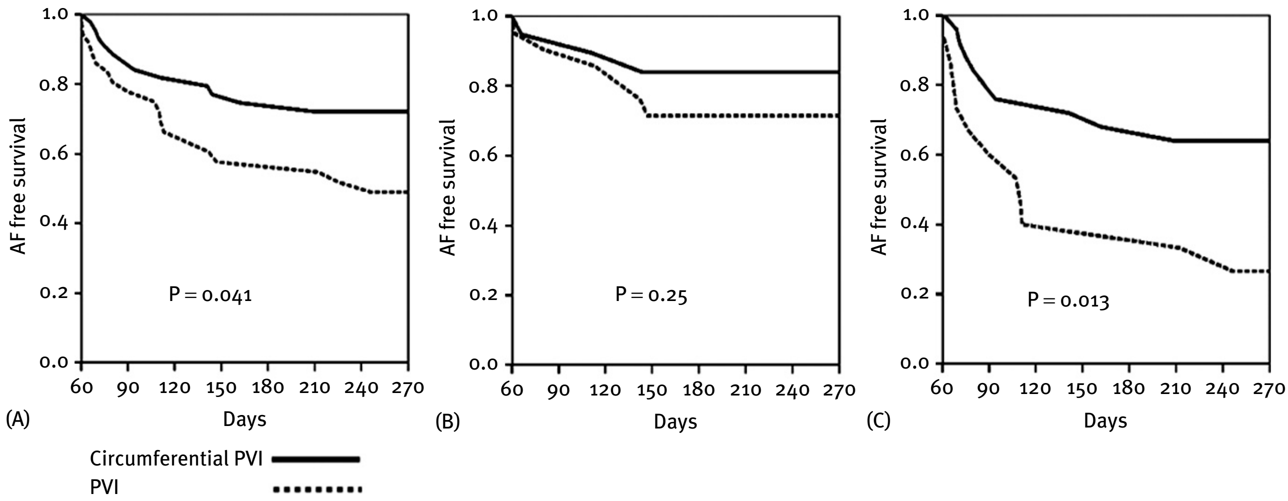

Figure . Kaplan-Meier estimates of arrhythmia symptom-free survival after circumferential pulmonary vein isolation (solid line) and pulmonary vein isolation (dashed line). (A) Kaplan-Meier curves in patients overall; (B) in those with left atrial volume index <27 ml/m²; (C) and in those with left atrial volume index ≥27 ml/m².

Table 2. Univariate Predictors of Late Recurrence in Patients Overall

	HR	95% CI	*P* Value
Age	0.99	0.97–1.03	.94
Sex	1.6	0.65–3.92	.31
Alcohol	1.13	0.53–2.41	.76
Diabetes	0.84	0.2–3.53	.84
Hypertension	1.2	0.12–0.85	.04
Body mass index	0.93	0.79–1.1	.41
Persistent AF	4.08	1.98–8.39	<.001
Duration of AF	1.05	0.89–1.11	.14
PVI	2.1	1.01–4.36	.047
ERAF	2.63	1.28–5.4	.008
EF	0.9	0.9–0.99	.027
LA volume index ≥27 ml/m²	2.57	1.2–5.5	.015

Abbreviations: AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; ERAF = early recurrence of atrial fibrillation; HR = hazard ratio; LA = left atrial; PVI = pulmonary vein isolation.

recurrence. Covariates identified with $P<.1$ by univariate analysis were included in a multivariate model. A forward stepwise selection procedure was used to the relative role of prognostic factors. A value of $P<.05$ was considered statistically significant.

Results

Baseline Characteristics

The 81 patients underwent PVI (n = 36) or circumferential PVI (n = 45) without respect to the echocardiographic results for LA volume index or type of AF (paroxysmal vs persistent AF). Of the 81 patients, 41 patients (50.7%) had less dilated LA (group 1; LA volume index <27cc/m^2) and 40 patients (49.3%) had dilated LA (group 2; LA volume index ≥27cc/m^2).

Procedural Characteristics

The mean total duration of the procedure was 240 ± 93 minutes for PVI compared with 251 ± 89 minutes for circumferential PVI ($P = .61$). The mean total fluoroscopy times were 72 ± 35 minutes for PVI compared with 79 ± 28 minutes for circumferential PVI ($P = .33$). Total ablation time was 128 ± 71 minutes for the PVI approach and 145 ± 64 minutes for the circumferential PVI approach ($P = .34$).

Univariate Predictors of Late Recurrence

All patients participated in all 9 months of follow-up, and no patient died during this period. At the 9-month follow-up, 18 patients (50%) after PVI and 33 patients (73.3%) after circumferential PVI were free of arrhythmia ($P = .037$; Table 1). Table 2 shows the univariate analysis of preprocedural variables and the risk of late recurrence. The risk of late recurrence was associated with persistent AF (hazard ratio [HR]: 4.08, 95% confidence interval [CI]: 1.98–8.38, $P<.001$), ERAF (HR: 2.63, 95% CI: 1.28–5.41, $P = .008$), LA volume index ≥27 ml/m^2 (HR: 2.57, 95% CI: 1.2–5.51, $P = .015$), PVI (HR: 2.1, 95% CI: 1.011–4.36,

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20567

Table 3. Univariate Predictors of Late Recurrence According to Left Atrial Volume

	Group 1 (LA Volume Index <27 ml/m²)			Group 2 (LA Volume Index ≥27 ml/m²)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	0.99	0.93–1.05	.76	0.97	0.92–1.03	.29
Sex	1.57	0.33–7.46	.57	1.69	0.56–5.10	.35
Alcohol	1.98	0.57–6.84	.28	0.92	0.33–2.53	.87
Diabetes	0.04	0–7.3	.53	0.63	0.33–6.18	.63
Hypertension	0.9	0.11–2.53	.43	1.26	0.058–0.68	.03
Body mass index	0.42	0.08–2.16	.29	0.89	0.73–1.1	.28
Persistent AF	1.67	0.35–7.87	.51	4.68	1.78–12.27	.002
Duration of AF	1.1	0.99–1.16	.1	1.1	0.94–1.22	.34
PVI	2.17	0.56–8.4	.26	2.92	0.12–7.08	.018
ERAF	7.14	1.83–27.92	.005	1.5	0.61–3.69	.37
EF	0.91	0.84–0.1	.041	0.96	0.91–1.02	.17
LA volume index	0.94	0.83–1.08	.39	1.03	0.98–1.08	.23

Abbreviation: AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; ERAF = early recurrence of atrial fibrillation; HR = hazard ratio; LA = left atrial; PVI = pulmonary vein isolation.

Table 4. Multivariate Analysis of Late Recurrence in Patients Overall

	HR	95% CI	*P* Value
Age	0.97	0.93–1.05	.12
Hypertension	1.1	0.14–1.33	.14
Persistent AF	2.76	1.15–6.65	.023
PVI	1.91	0.84–4.33	.12
ERAF	2.80	1.07–7.1	.012
EF	0.99	0.94–1.05	.74
LA volume Index ≥27 ml/m²	2.76	1.07–1.05	.036

Abbreviation: AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; ERAF = early recurrence of atrial fibrillation; HR = hazard ratio; LA = left atrial; PVI = pulmonary vein isolation.

$P = .047$), lower LV ejection fraction (HR: 0.95, 95% CI: 0.91–0.99, $P = .027$), and hypertension (HR: 1.2, 95% CI: 0.12–0.85, $P = .04$).

Table 3 shows the univariate analysis according to LA volume. In group 1, the risk of late recurrence showed an increase with ERAF (HR: 7.14, 95% CI: 1.83–27.92, $P = .005$) and lower ejection fraction (HR: 0.91, 95% CI: 0.84–27.92, $P = .041$). In contrast, in group 2, persistent AF (HR: 4.68, 95% CI: 1.78–12.27, $P = .002$), PVI (HR: 2.92, 95% CI: 0.12–7.08, $P = .018$), and hypertension (HR: 1.26, 95% CI: 0.06–0.68, $P = .03$) were associated with late recurrence. Kaplan-Meier curves describing late recurrence in all patients and subgroups are depicted in the Figure.

Multivariate Predictors of Late AF Recurrence

Univariate variables with $P<.1$ were entered into the Cox model. Independent predictors of late recurrence of AF, their hazard ratios, and 95% confidence intervals are shown in Table 4. In patients overall, ERAF (HR: 2.8, 95% CI: 1.07–7.1, $P = .012$), persistent AF (HR: 2.76, 95% CI: 1.15–6.65, $P = .023$), and LA volume index ≥ 27 ml/m^2 (HR: 2.76, 95% CI: 1.07–1.046, $P = .036$) were independent predictors of late recurrence. In group 1, ERAF (HR: 13.36, 95% CI: 2.51–71.24, $P = .002$) was an independent predictor, whereas persistent AF (HR: 6.05, 95% CI: 1.85–19.77, $P = .003$), and PVI (HR: 5.6, 95% CI: 1.9–16.56) were significant independent predictors of late recurrence in group 2 (Table 5).

Discussion

We evaluated the medium-term outcomes of 81 procedures in symptomatic patients with paroxysmal or persistent AF resistant to class I and III antiarrhythmic drugs who underwent PVI or circumferential PVI. In this study, symptomatic AF was eliminated more reliably by circumferential PVI than by PVI, but LA volume also

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20567

Table 5. Multivariate Analysis of Late Recurrence in Patients with LA Volume Index <27 ml/m² or ≥ 27 ml/m²

	Group 1 (LA Volume Index <27 ml/m²)			Group 2 (LA Volume Index ≥27 ml/m²)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	0.97	0.91–1.03	.33	0.95	0.90–1.01	.11
Hypertension				1.08	0.16–2.9	.68
Persistent AF				6.05	1.85–19.78	.003
PVI				5.6	1.9–16.56	.002
ERAF	8.46	2.07–34.52	.003			

Abbreviation: AF = atrial fibrillation; CI = confidence interval; EF = ejection fraction; ERAF = early recurrence of atrial fibrillation; HR = hazard ratio; LA = left atrial; PVI = pulmonary vein isolation.

influenced the efficacy of the 2 techniques. Circumferential PVI was more effective than PVI only in patients with a structural change of atria, that is, a dilated LA chamber. In contrast, there was no statistically significant difference in efficacy between the 2 procedures in patients with a less dilated LA. To the best of our knowledge, this is the first study to report a relationship between LA size and the effectiveness of these 2 procedures.

Large population-based studies have established atrial dilation as an independent risk factor for the development of AF.[17,18] An increase in atrial size increases the possible number of multiple wavelets during AF. Perpetuation of AF is promoted by an atrial substrate that favors initiation and continuation of reentering wavelets. Dilated atria show more spatial heterogeneities in conduction and a higher incidence of conduction disturbances compared with less dilated atria in a goat model.[19] Disturbances in conduction are usually attributed to increased interstitial deposition of collagen (fibrosis).[20–22] In addition, Verma et al[23] found an association of atrial fibrosis, as an anatomical substrate of AF, with larger LA size in patients with AF. Ikeda et al[24] described the effects of anatomic obstacles on the meandering of reentrant wave fronts. These previous studies suggest that relatively less dilated atria would have less structural arrhythmogenic substrate. Beukema et al[6] reported that the extent of myocardial damage incurred by ablation correlates with an arrhythmia-free outcome in circumferential LA ablation. A wide reduction of substrate by circumferential LA ablation may be effective only in dilated atria with much more structural substrates. In contrast, a "wide area" ablation may be unnecessary in less dilated LA with scarce structural substrates.

Catheter ablation of AF continues to evolve. Although the mechanism behind AF is multifactorial,[25] individual technical approaches to date have not been based on the pathophysiological characteristics of AF. Targeted design of individual interventional treatments based on pathophysiological characteristics such as anatomical and electrical substrate or autonomic nervous activity is needed to eliminate the initiation and/or maintenance of AF in future. Our findings suggest that treatment strategies should be individualized according to LA size for more successful outcomes. The interventional approach in dilated LA cases should focus on wide reduction of electroanatomical substrates. However, in less dilated atria, "segmental ablation" rather than "wide ablation" may be sufficient for a successful outcome. This study suggests that the targeted treatment based on LA size will be helpful to reduce unnecessary wide ablation and the complications arising from wide excision in treating patients with a small LA chamber, even though our study is limited by small sample size. Many targeted treatments based on pathophysiological mechanisms or characteristics of the individual patient in AF ablation should be developed in the future.

Several limitations of our study must be acknowledged. Our study consisted of a relatively small patient population, but we felt that it was not ethical to continue to perform PVI after finding that it was less effective in patients with an enlarged LA. In addition, we did not perform echocardiography after ablation, and so we did not measure LA size change following each procedure.

In conclusion, circumferential PVI may be more effective than PVI in patients with structurally changed atria, that is, a dilated LA, but the efficacy of the 2 procedures does not appear to differ in patients with less dilated LA.

Acknowledgment

Drs HJ Hwang and JM Lee contributed equally to this work

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Published online in Wiley InterScience. (www.interscience.wiley.com)
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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20567