Prolonged PR Interval and Risk of Recurrence of Atrial Fibrillation After Catheter Ablation

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SUMMARY

It has been demonstrated that a prolonged PR interval is associated with an increased risk of AF. However, the impact of a prolonged PR interval on recurrence of paroxysmal atrial fibrillation (AF) after catheter ablation is not clear. A total of 112 patients with a prolonged PR interval (PR > 200 ms) (PPR group) and 112 age- and gender-matched control patients (on a 1:1 basis) with a normal PR interval (NPR group) were included in this study. AF recurrence was defined as the occurrence of confirmed atrial tachyarrhythmia lasting more than 30 seconds beyond 3 months after catheter ablation in the absence of any antiarrhythmic treatment. During a mean follow-up period of 10.9 ± 5.5 months (range, 3–18 months), 61 patients (27.2%) developed recurrence of AF. The recurrence rate was higher in the PPR group than in the NPR group (33.9% versus 20.5%, respectively; $P = 0.018$). Cox regression analysis with adjustment for age, body mass index, valvular heart disease, left atrial diameter, and pulmonary vein isolation identified only a prolonged PR interval as an independent predictor of recurrence of AF (hazard ratio, 1.81; 95% confidence interval, 1.07–3.05; $P = 0.027$). Patients with a prolonged PR interval were at an increased risk of AF recurrence after catheter ablation. (Int Heart J 2014; 55: 126-130)

Key words: Atrial tachyarrhythmia

Atrial fibrillation (AF) is a common cardiac arrhythmia in the general population¹⁾ and is associated with increased cardiovascular morbidity and mortality.^{2,3)} A recent post hoc analysis of a Danish multicenter randomized trial (DANPACE trial) showed that a prolonged PR interval is associated with an increased risk of AF in patients with sick sinus syndrome.⁴⁾ These results are in accordance with the findings of a large community-based cohort study in which a PR interval longer than 200 ms was associated with a doubled risk of later AF compared with a shorter PR interval.⁵⁾ Catheter ablation has been established as an effective therapy for drug-refractory paroxysmal AF. However, there is still a risk of recurrence after ablation. Previous studies have examined some predictors of AF recurrence.^{6,7)} However, there is little information available about the impact of a prolonged PR interval on recurrence of AF after catheter ablation. In patients with a prolonged PR interval, most of the pathogenic factors for AF persist after ablation. Therefore, it is reasonable to hypothesize that a prolonged PR interval increases the risk of recurrence of AF. This retrospective study evaluated the impact of a prolonged PR interval on recurrence of AF after catheter ablation.

METHODS

Study subjects: We reviewed the records of 1593 consecutive patients with refractory symptomatic paroxysmal AF who had been prospectively entered into our database. All of these patients were referred to Beijing An Zhen Hospital, Capital Medical University for first-time circumferential pulmonary vein (PV) radiofrequency ablation from January 2008 to December 2012. The PR interval was considered to be prolonged if it was > 200 ms and to be normal if it was ≤ 200 ms as determined from a resting 12-lead electrocardiogram after all antiarrhythmic drugs had been discontinued for at least 5 half-lives and in the absence of β -blocker and calcium channel blocker use. Of the 1593 patients, 112 had a prolonged PR interval or first-degree atrioventricular block. These patients were enrolled in the study (PPR group) together with 112 age- and gender-matched patients (on a 1:1 basis) with a normal PR interval (PR ≤ 200 ms) (NPR group). All patients provided written informed consent, and the study was approved by the institutional review board. Transesophageal and transthoracic echocardiography images were obtained prior to ablation to measure the left atrial (LA) anteroposterior diameter, left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, and LV ejection fraction and to exclude the presence of intra-atrial thrombus.

Electrophysiological study and catheter ablation: The ablation

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Received for publication August 11, 2013. Revised and accepted September 28, 2013.

Released advance online J-STAGE March 14, 2014.

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Table I. Characteristics of Patients in the PPR and NPR Groups

	PPR (<i>n</i> = 112)	NPR (<i>n</i> = 112)	<i>P</i>
Age (years)	61 ± 11	61 ± 11	1.00
Male, <i>n</i> (%)	76 (67.9%)	76 (67.9%)	1.00
BMI (kg/m ²)	25.9 ± 3.1	25.7 ± 3.0	0.623
AF duration (years)	6.3 ± 4.3	6.5 ± 4.1	0.780
Heart rate (beats/minute)	69 ± 10	68 ± 9	0.434
DM, <i>n</i> (%)	21 (18.8%)	10 (8.9%)	0.033
Hypertension, <i>n</i> (%)	55 (49.1%)	62 (55.4%)	0.349
Heart failure, <i>n</i> (%)	2 (1.8%)	3 (2.7%)	0.651
Valvular heart disease, <i>n</i> (%)	32 (28.6%)	15 (13.4%)	0.005
CAD, <i>n</i> (%)	2 (10.7%)	9 (8.0%)	0.492
Left atrial diameter (mm)	39.3 ± 5.9	37.9 ± 4.9	0.025
LVEDD (mm)	48.3 ± 5.6	47.9 ± 5.2	0.502
LVESD (mm)	32.0 ± 4.5	31.7 ± 4.6	0.574
Ejection fraction (%)	62.9 ± 9.4	63.2 ± 9.0	0.731
ACEI/ARB, <i>n</i> (%)	40 (35.7%)	33 (29.5%)	0.318
Statins, <i>n</i> (%)	32 (28.6%)	22 (19.6%)	0.118
Pulmonary vein isolation, <i>n</i> (%)	109 (97.3%)	110 (98.2%)	0.651

BMI indicates body mass index; AF, atrial fibrillation; DM, diabetes mellitus; CAD, coronary artery disease; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; ACEI, angiotensin-converting enzyme inhibitors; and ARB, angiotensin receptor blockers.

procedure was performed in the postabsorptive state under conscious sedation. We employed the technique of circumferential PV ablation guided by 3-dimensional left atrial mapping, which was described previously in detail.^{8,9)} Briefly, the LA was explored using a trans-septal approach. The LA geometry was reconstructed with a 3.5-mm tip ablation catheter (NaviStar ThermoCool; Biosense Webster, USA) in a CARTO system. Continuous irrigated radiofrequency ablation was performed along each PV antrum to encircle the ipsilateral PVs (target temperature, 43°C; maximum power, 35 W; infusion rate, 17 mL/min). The procedural endpoints were completeness of continuous circular lesions and electrical isolation of all PVs as identified by a decapolar circumferential mapping catheter (Lasso; Biosense Webster). If a typical atrial flutter had been documented before the procedure, the tricuspid isthmus responsible for this tachycardia was identified and ablated.

Postablation management and follow-up: After the procedure, all patients received antiarrhythmic drugs if there were neither contraindications nor intolerance. If no recurrent atrial tachyarrhythmia occurred after 2 or 3 months, the drug treatment was discontinued. All asymptomatic patients were followed up with a 12-lead electrocardiogram and 24-hour Holter recordings at the 1st, 3rd, 6th, and 12th month and every 6 months beyond 1 year after the ablation procedure. If the patient was symptomatic, a new electrocardiogram or 24-hour Holter recording was obtained. Recurrence was defined as the occurrence of confirmed atrial tachyarrhythmia lasting more than 30 seconds (documented by electrocardiogram or Holter recordings) beyond 3 months after the catheter ablation in the absence of any antiarrhythmic treatment.

Statistical analysis: All analyses were performed with SPSS software version 17.0. Continuous data are presented as the mean ± standard deviation. Univariate analysis to assess the predictive value of clinical variables on AF recurrence was performed using the unpaired independent-samples *t*-test for continuous variables and the χ^2 test and Fisher's exact test if necessary for categorical variables. A Kaplan–Meier estimation with a log-rank test was performed for unadjusted analysis

Figure. Kaplan–Meier curves showing recurrence in patients with prolonged and normal PR intervals. Patients with a prolonged PR interval had a higher incidence of recurrence of atrial tachyarrhythmia (ATA) than did patients with a normal PR interval (33.9% versus 20.5%, respectively; *P* = 0.018 by log-rank test).

of the impact of a prolonged PR interval on recurrence of AF. Cox proportional hazards regression was employed to examine the risks for recurrence. Age, body mass index (BMI), valvular heart disease, LA diameter, and PV isolation were adjusted in the Cox analysis. All probability values were 2-sided, and a *P* of < 0.05 was considered significant.

RESULTS

Clinical characteristics of patients with prolonged and normal PR intervals: The clinical characteristics of patients in the PPR and NPR groups are shown in Table I. The prevalences of

Table II. Characteristics of Patients With and Without Recurrence of AF

	Recurrence (<i>n</i> = 61)	Non-recurrence (<i>n</i> = 163)	<i>P</i>
Age (years)	62 ± 11	61 ± 11	0.347
Male, <i>n</i> (%)	43 (70.5%)	109 (66.9%)	0.605
BMI (kg/m ²)	26.2 ± 3.1	25.7 ± 3.0	0.357
AF duration (years)	6.3 ± 4.4	6.4 ± 4.1	0.821
DM, <i>n</i> (%)	10 (16.4%)	21 (12.9%)	0.231
Hypertension, <i>n</i> (%)	35 (57.4%)	82 (50.3%)	0.346
Heart failure, <i>n</i> (%)	2 (3.3%)	3 (1.8%)	0.615
Valvular heart disease, <i>n</i> (%)	15 (24.6%)	32 (19.6%)	0.488
CAD, <i>n</i> (%)	7 (11.5%)	14 (8.6%)	0.509
Left atrial diameter (mm)	39.0 ± 5.6	38.2 ± 5.2	0.281
LVEDD (mm)	48.5 ± 5.1	48.0 ± 5.4	0.468
LVESD (mm)	31.6 ± 4.8	31.8 ± 4.5	0.714
Ejection fraction (%)	62.4 ± 11.0	63.3 ± 8.7	0.525
ACEI/ARB, <i>n</i> (%)	23 (37.7%)	50 (30.7%)	0.318
Statins, <i>n</i> (%)	13 (21.3%)	41 (25.2%)	0.550
PPR, <i>n</i> (%)	38 (62.3%)	74 (45.4%)	0.024
Pulmonary vein isolation, <i>n</i> (%)	59 (96.7%)	160 (98.2%)	0.503

PPR indicates prolonged PR interval. For other abbreviations, see Table I.

Table III. Prolonged PR Interval and Recurrence of AF in Multivariate Analysis

Variables	<i>P</i>	HR (95%CI)
Age	0.262	1.01 (0.99-1.04)
BMI	0.124	1.07 (0.98-1.15)
Valvular heart disease	0.453	1.25 (0.69-2.27)
Left atrial diameter	0.596	1.01 (0.97-1.06)
Pulmonary vein isolation	0.718	1.30 (0.31-5.44)
PPR	0.027	1.81 (1.07-3.05)

HR indicates hazard ratio and CI, confidence interval.

diabetes mellitus and valvular heart disease were significantly higher in the PPR group than in the NPR group. The LA diameter was significantly larger in the PPR group than in the NPR group. Age, gender, AF duration, heart rate, LV ejection fraction, LV end-diastolic dimension, and LV end-systolic dimension were not significantly different between the 2 groups. The prevalences of hypertension, coronary artery disease, and medication use (β -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins) were not significantly different between the 2 groups.

Recurrence of AF in patients with a prolonged PR interval: During the mean follow-up period of 10.9 ± 5.5 months (range, 3–18 months), 61 patients (27.2%) developed recurrence of AF. The recurrence rate was 33.9% in the PPR group and 20.5% in the NPR group (*P* = 0.018) (Figure). The characteristics of patients with and without recurrence are shown in Table II. Univariate analyses found that a prolonged PR interval was the only predictor of recurrence of AF. Cox regression analysis with adjustment for age, BMI, valvular heart disease, LA diameter, and PV isolation identified only a prolonged PR interval as an independent predictor of recurrence of AF (hazard ratio, 1.81; 95% confidence interval, 1.07–3.05; *P* = 0.027) (Table III).

DISCUSSION

The main finding of the present study is that a prolonged

PR interval is an independent predictor of recurrence of AF in patients who have undergone catheter ablation for paroxysmal AF.

Several studies have demonstrated that a prolonged PR interval is associated with an increased risk of AF.^{2,4,5,10} The exact mechanism for this is unknown. The PR interval is determined by the conduction time from the sinus node to the ventricles and thus integrates information about a number of sites in the conduction system of the heart. Prolongation of the PR interval may result from a conduction delay in the atrium, atrioventricular node, and/or His-Purkinje system. Although prolongation of the PR interval usually involves a conduction delay in the atrioventricular node, it is frequently accompanied by a conduction delay in the atrium as well.^{11,12} The total atrial conduction time was recently found to be a very strong predictor of AF.^{13,14} The prolonged PR interval probably also reflects a prolonged atrial conduction time that is likely caused by atrial fibrosis and atrial dilatation, which may be involved in the substrate for AF.⁴ In addition, a prolonged PR interval results in delayed and ineffective mitral valve closure and diastolic mitral regurgitation,¹⁵ especially when the PR interval exceeds 230 ms,¹⁶ which promotes increased LA pressure. Increased LA pressure has been shown to be associated with AF.^{17,18}

In patients with a prolonged PR interval, most of the pathogenic factors causing AF remain after ablation. It is therefore reasonable to believe that a prolonged PR interval lowers the success rate of catheter ablation for AF. In this study, we sought to address the outcome of catheter ablation for AF in patients with a prolonged PR interval. To the best of our knowledge, our data show for the first time that a prolonged PR interval increases the incidence of recurrence after catheter ablation for paroxysmal AF in both univariate and multivariate analyses. Several mechanisms may account for the relationship between a prolonged PR interval and recurrence of AF. First, the prolonged PR interval probably reflects underlying atrial disease with atrial fibrosis or atrial dilatation. Atrial fibrosis¹⁹⁻²¹ and atrial dilatation²²⁻²⁴ are associated with increased recurrence of AF after catheter ablation. Second, a prolonged PR interval results in increased LA pressure, delayed and ineffective mitral valve closure, and diastolic mitral regurgitation.¹⁵ Fur-

thermore, in patients with a very long PR interval, a short coupling between ventricular and atrial activation can also occur, which may cause atrial contraction against closed AV valves. These factors contribute to increased LA pressure. Geske, *et al* reported that increased LA pressure was associated with increased LA size.²⁵⁾ The LA size is a well-known predictor of recurrence after catheter ablation for AF.²²⁻²⁴⁾ In addition, mechanoelectric feedback²⁶⁾ and proliferation of arrhythmogenic fibroblasts^{27,28)} secondary to increased LA pressure may also play a role in promoting recurrence of AF. Third, a prolonged PR interval is associated with endothelial dysfunction. Recent studies showed that PR interval prolongation, even in the conventionally normal range, is independently associated with endothelial dysfunction.^{29,30)} Endothelial dysfunction is an important predictor for recurrence of AF after catheter ablation.²²⁾

In the present study, patients in the PPR group had a larger LA size than did patients in the NPR group. As mentioned above, LA size is a well-known predictor of recurrence of AF after catheter ablation.²²⁻²⁴⁾ However, after adjusting for the LA diameter, a prolonged PR interval was identified as an independent predictor of recurrence of AF. This may be explained by a recent study¹⁹⁾ showing that whereas patients with a severely enlarged LA may be accurately identified as being at high risk for AF recurrence, patients with mild to moderate LA enlargement show varying responses to catheter ablation. Another likely explanation for this is that when LA dilation inclines to asymmetry, the LA volume may be superior to the LA diameter in terms of predicting recurrence of AF.^{31,32)}

As mentioned above, the patients with the prolonged PR interval probably suffered from atrial disease with atrial fibrosis or atrial dilatation, which may be involved in the substrate for AF. Therefore, it seemed to be reasonable that the paroxysmal AF patients with the prolonged PR interval have higher recurrence of AF after single circumferential PV ablation. For these patients, circumferential PV ablation alone may be insufficient. However, whether additional substrate ablation strategies such as left atrial linear lesions or ablation of complex fractionated atrial electrograms are required for these patients to achieve a higher success rate was not determined in this study, and this needs further studies.

Several limitations of this study should be noted. First, because the PR interval was measured from the surface electrocardiogram as opposed to an intracardiac recording, the relative contributions of delays at different conduction sites could not be assessed. Second, because atrial fibrosis was not assessed using delayed enhancement magnetic resonance imaging²⁰⁾ or 2-dimensional echocardiography derived integrated backscatter¹⁹⁾ for all patients, whether the patients with a prolonged PR interval suffered from atrial fibrosis was not determined in this study. Third, the autonomic nervous system, which may be closely related to PR interval and cannot be tested in this study, should warrant further investigation. Fourth, PV reconnection is a known cause of AF recurrence.^{33,34)} The rate of PV isolation did not differ between the PPR and NPR groups, but this study did not determine whether a prolonged PR interval was associated with an increased likelihood of PV reconnection because it is not clear how many patients with AF recurrence had PV reconnections in two groups. Finally, the diagnosis of recurrence was based on symptoms, ECG, and Holter-ECG findings. The rate of recurrence of AF might have

been underestimated because some patients were asymptomatic.

In conclusion, this study is the first to report that a prolonged PR interval is an independent predictor of recurrence of AF in patients who have undergone catheter ablation.

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