Associations Between Renal Function, Atrial Substrate Properties and Outcome of Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation

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Background: Renal dysfunction was reported to be associated with a higher recurrence rate after electric cardioversion of atrial fibrillation (AF). The aim of this study was to investigate the associations between renal function, atrial substrate properties and outcome of catheter ablation in paroxysmal AF patients.

Methods and Results: A total of 232 paroxysmal AF patients that underwent catheter ablation were enrolled in the study. The estimated glomerular filtration rate (GFR) was calculated using the Cockcroft–Gaut equation normalized by the body surface area, and the patients were divided into 3 groups according to their GFR (group 1: ≥90 ml·min⁻¹·1.73 m⁻², group 2: 60–90 ml·min⁻¹·1.73 m⁻² and group 3: <60 ml·min⁻¹·1.73 m⁻²). The left atrial (LA) voltage became lower and the activation time longer when the GFR decreased from group 1 to group 3. During a follow-up of 25.4±13.3 months, 15.9% of the study population suffered from AF recurrences. The recurrence rates of those 3 groups were 6.9%, 14.5% and 38.9%, respectively. The LA dimension, LA voltage and groups of renal function were identified to be the independent predictors of an AF recurrence in the multivariate analysis.

Conclusions: A decreased GFR was associated with an abnormal LA substrate and high recurrence rate of catheter ablation in patients with paroxysmal AF. (Circ J 2011; 75: 2326–2332)

Key Words: Atrial fibrillation; Catheter ablation; Renal function

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with marked morbidity, mortality, and socioeconomic burden.¹–³ A previous study demonstrated that the prevalence of AF gradually increased with a decreasing glomerular filtration rate (GFR) and was 2–3 times that reported in the general population.⁴,⁵ Furthermore, the progression of renal dysfunction was a powerful predictor of new-onset AF in hypertensive patients.⁶ Recently, an impaired renal function, defined by the estimated GFR (eGFR), was reported to be associated with an increased risk of AF recurrence after successful electric cardioversion.⁷ In regard to the treatment of AF, catheter ablation provides an effective therapy for patients with symptomatic and drug-refractory AF, with an acceptably low incidence of complications.⁸–¹⁰ The purpose of this study was to investigate the association of renal function with the atrial substrate properties and outcome of catheter ablation in paroxysmal AF patients.

Methods

A total 232 consecutive patients (age 53.4±11.6 years old, 168 males) with paroxysmal AF who received catheter ablation for the first time were enrolled. Bi-atrial electroanatomic mapping using a three-dimensional system (NavX, St Jude Medical Inc, MN, USA) was performed in each patient with symptomatic drug refractory paroxysmal AF (<7 days) who underwent radiofrequency catheter ablation. The right atrial (RA) and left atrial (LA) bipolar peak-to-peak voltage and total activation time were obtained during sinus rhythm. The LA diameter and left ventricular ejection fraction were measured by transthoracic echocardiography, according to the American Society of Echocardiography criteria.¹² The estimated GFR was calculated for each patient.

Calculations and Classifications of the GFR

The estimated GFR was calculated using the Cockcroft–Gaut

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Figure 1. Examples of right atrial (A) and left atrial (B) voltage maps. The voltage of the atrium is represented by different colors. The gray and purple areas represent the low voltage zones (<0.5 mV) and normal voltage zones (>2 mV), respectively. SVC, superior vena cava; IVC, inferior vena cava; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; LAA, left atrium appendage; MV, mitral valve; TV, tricuspid valve.
equation, normalized by the body surface area (BSA) (ml·min⁻¹·1.73m⁻²) in each patient. The blood samples for analysis of the GFR were drawn 1 day before the catheter ablation.

(a) For men: eGFR = (140 – Age (years)) × body weight (kg) × 1.73(m²)/serum Creatinine (mg/dl) × 72 × BSA (m²)
(b) For women: eGFR = (140 – Age (years)) × body weight (kg) × 1.73(m²) × 0.85/serum Creatinine (mg/dl) × 72 × BSA (m²)

The patients were divided into 3 groups according to their eGFR (Group 1 ≥90 ml·min⁻¹·1.73m⁻²; Group 2, 60–90 ml·min⁻¹·1.73m⁻²; and Group 3, <60 ml·min⁻¹·1.73m⁻²). Group 1 (normal GFR), group 2 (mildly decreased GFR) and group 3 (moderately-severely decreased GFR) included 72, 124 and 36 patients, respectively.

Electroanatomic Mapping, Catheter Ablation and Follow up
Each patient underwent an electrophysiological study and catheter ablation in the fasting, non-sedative state after written informed consent was obtained. The details have been described previously. In brief, after completing the RA and LA geometry, a sequential contact voltage map was constructed in all patients during sinus rhythm. For the patients with an AF occurrence during the procedure, external direct

<table>
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<tr>
<th>Table 1. Baseline Characteristics of Patients</th>
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<td>Group 1 (n=72)</td>
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<td>Age, years</td>
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<tr>
<td>Male, %</td>
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<tr>
<td>Medical history, %</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<td>Coronary artery disease</td>
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<td>ACEIs or ARBs</td>
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<td>Statins</td>
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<td>Body mass index, kg/m²</td>
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<td>Laboratory examinations</td>
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<td>Total cholesterol, mg/dl</td>
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<td>LDL-cholesterol, mg/dl</td>
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<td>HDL-cholesterol, mg/dl</td>
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<td>Triglyceride, mg/dl</td>
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<td>eGFR, ml·min⁻¹·1.73m⁻²</td>
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<tr>
<td>Left atrial diameter, mm</td>
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<td>LVEF, %</td>
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<td>AF duration, years</td>
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Group 1: eGFR ≥90ml·min⁻¹·1.73m⁻²; Group 2: 90>eGFR ≥60ml·min⁻¹·1.73m⁻²; Group 3: eGFR <60ml·min⁻¹·1.73m⁻². ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; AF, atrial fibrillation. *P value <0.05, group 2 or 3 vs. group 1; **P value <0.05, group 3 vs. group 2.

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<th>Table 2. Bi-Atrial Substrate Electrophysiological Properties of the Patients</th>
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<tr>
<td>Group 1 (n=72)</td>
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<td>RA total activation time, ms</td>
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<td>RA voltage, mV</td>
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<tr>
<td>LA total activation time, ms</td>
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<td>LA voltage, mV</td>
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RA, right atrium; LA, left atrium. *P value <0.05, group 2 or 3 vs. group 1; **P value <0.05, group 3 vs. group 2.

![Figure 2. Atrial fibrillation (AF) recurrence rate after the catheter ablation in the patients with different renal function levels. Group 1, eGFR ≥90ml·min⁻¹·1.73m⁻²; Group 2, 90>eGFR ≥60ml·min⁻¹·1.73m⁻²; and Group 3, eGFR <60ml·min⁻¹·1.73m⁻². eGFR, estimated glomerular filtration rate.](image-url)
current cardioversion was performed to convert the patients to sinus rhythm before mapping was performed. The recordings from the coronary sinus catheter electrodes were used to provide a timing reference signal during the mapping procedure. A 4-mm tipped ablation catheter was used to collect the local activation time (relative to the reference signal) and voltages while the catheter came in contact with the atrial wall as it was swiped throughout the atrium during sinus rhythm. After completion of the sequential map, the bipolar mapping points were analyzed by offline software. Examples of the RA and LA voltage maps are shown in Figure 1.

Continuous circumferential lesions were created encircling the right and left pulmonary vein (PV) ostia guided by the NavX system using either a conventional 4-mm-tip or an internal irrigated-tip catheter. The intention was to place the radiofrequency lesions at least 1–2 cm away from the angiographically defined ostia. Successful circumferential PV isolation was demonstrated by the absence of any PV activity or dissociated PV activity. The requirement of additional ablation was assessed based on the AF inducibility.

After completing the PV isolation, the ablation was only applied to spontaneously initiating focal atrial tachycardias and non-PV ectopy that initiated AF. The methods of the identification of the non-PV ectopy have been described in our previous publications. Among the study population, 13.4% had non-PV triggers and received ablations. There were no significant differences about the presences of non-PV triggers in these 3 groups (group 1=12.5%; group 2=14.5%; group 3=11.1%; P value=0.839).

After the catheter ablation, all patients received oral amiodarone for 8 weeks to prevent the early recurrence of paroxysmal AF (defined as <1 month after the ablation). If the patients could not tolerate amiodarone, propafenone or flecainide was used in those patients. After discharge, the patients underwent follow up (2 weeks after the catheter ablation, then every 1–3 months) at our cardiology clinic or with the referring physicians. During each follow up after the ablation, 24-h Holter monitoring and/or cardiac event recording with a recording duration of 1 week were performed. AF recurrence was defined as an episode lasting more than 1 min, and was confirmed by electrocardiograms 2 months after the ablation (blanking period). The long-term efficacy was assessed clinically on the basis of the clinical symptoms, resting surface 12-lead electrocardiogram, and 24-h Holter monitoring and/or 1 week cardiac event recordings.

Statistical Analysis
The data are presented as mean values and standard deviations for normally distributed continuous variables and proportions for categorical variables. The differences between the continuous values were assessed using an unpaired 2-tailed t-test or 1-way analysis of variance Post Hoc Bonferroni test for normally distributed continuous variables, Mann-Whitney rank-sum test for skewed variables, and chi-squared test for nominal variables. Because of significant age and gender differences among the 3 groups, the estimated marginal mean values were used for adjusting the LA voltage, LA total activation time, RA voltage and RA total activation time for age and gender. A Bonferroni adjustment was applied for multiple comparisons between these 3 groups. The AF recurrence-free survival curve was plotted via the Kaplan-Meier method with statistical significance examined by the log-rank test. A univariate Cox regression analysis of the various clinical variables was performed to determine the predictors of recurrence after the catheter ablation of AF. The variables selected to be tested in the multivariate analysis were those with P values <0.1 in the univariate models. All statistical significances were set at a P value <0.05 and all statistical analyses were carried out by using SPSS 17.0 software (SPSS Inc, USA).

Results
Clinical Characteristics
The baseline characteristics of the study patients are shown in Table 1. The mean age of the study population was 53.4±11.6 years (range, 23–77 years) with 168 men and 64 women. Among the study population, 35.3% had hypertension, 14.2% diabetes mellitus, 16.4% dyslipidemia and 14.2% coronary
The AF duration was 4.1 ± 3.9 years. The eGFRs of the 3 groups were 102.4 ± 10.7, 74.9 ± 9.0 and 48.9 ± 9.7 ml·min⁻¹·1.73 m⁻², respectively. The patients with a lower eGFR were older, consisted of more females, had a higher frequency of underlying disease (hypertension and coronary artery disease) and greater angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker use as compared to that of the patients with a higher eGFR. There were no significant differences in regard to the lipid profile and left ventricular ejection fraction between these 3 groups. However, the LA dimension was larger in group 3 as compared to that of group 1 and group 2. There was a significant correlation between the absolute value of eGFR and LA dimension (r=–0.313, P value <0.001).

Electrophysiological Properties of the Bi-Atrial Substrate

The electrophysiological properties of the bi-atrial substrate in the study patients are shown in Table 2.

**LA Voltage and Total Activation Time**

There were significant gradients of the LA voltage and activation time among these 3 groups. The LA voltage became lower and activation time longer when the GFR decreased from group 1 to group 3. These differences were still significant after adjusting for age and gender. The absolute value of GFR was also significantly correlated with LA voltage (r=0.454, P value <0.001) and total activation time (r=−0.378, P value <0.001).

**RA Voltage and Total Activation Time**

In contrast to the LA voltage, although the RA voltage decreased from group 1 to group 3, the differences were not statistically significant between each group. In regard to the activation time, it was longer in groups 2 and 3 as compared to that in group 1. These differences were still significant after adjusting for age and gender. However, no significant difference was noted between group 2 and group 3.

Factors Associated With AF Recurrence After Catheter Ablation

During the follow up period of 25.4 ± 13.3 months, 37 patients (15.9% of the study population) suffered from AF recurrences. The AF recurrence rate increased from 6.9% in group 1, 14.5% in group 2 to 38.9% in group 3 (Figure 2). The Kaplan-Meier curve of the freedom from an AF recurrence is shown in Figure 3. The predictors of an AF recurrence in univariate analysis included age, hypertension, LA dimension, left ventricular ejection fraction, LA voltage and renal function group (Table 3). The LA dimension, LA voltage and renal function group remained as independent predictors of an AF recurrence in the multivariate Cox regression analysis (Table 4).

Discussion

In this study, we investigated the association of the renal function to the atrial substrate properties determined via a mapping system and the outcome of the catheter ablation in paroxysmal AF patients. The main findings were as follows: (1) a decreased...
GFR was associated with arrhythmogenic substrate properties of the LA (low LA voltage and long activation time); and (2) a decreased GFR was associated with a poor prognosis after the catheter ablation of paroxysmal AF.

Renal Function, Atrial Substrate Properties and AF
The prevalence of AF was approximately 27% in patients with end-stage renal disease (ESRD) under long-term hemodialysis, and was higher than that in the general population. Among the patients with less severe chronic kidney disease who were not undergoing hemodialysis, the prevalence of AF was similar to that of the patients with ESRD. A recent study performed in Japan further demonstrated that the prevalence of AF gradually increased with a decreasing GFR, which was unrelated to the age increases. The findings of these previous studies suggest that processes influencing the development of AF likely occur early in the course of the decline in the GFR. In the current study, we showed that the LA voltage became lower and LA activation time longer when the GFR decreased from group 1 to group 3, and we also demonstrated a significant electrical gradient in the spectrum of a declining renal function. Even among the patients with a mildly decreased GFR (group 2), the LA substrate properties were worse than those in the patients with a normal GFR (group 1). However, there was no significant difference in the LA dimension between group 1 and group 2. That suggests that the electrical remodeling happened prior to the structural remodeling of the LA during the course of the deterioration of the renal function. Because the low voltage area might aggravate an interatrial conduction delay and prolong the activation time, resulting in the formation of circuits for reentry and thus promote the perpetuation of AF, the finding of our investigation provides a possible explanation for the clinical observation of an increasing AF prevalence from the early stage of renal dysfunction. Our study proved that even a mildly decreased GFR was associated with an arrhythmogenic LA substrate, which might lead to the susceptibility of an AF occurrence.

In comparison with LA, the differences of atrial substrate were not noted in the RA. The possible explanation was that renal dysfunction was associated with increased left ventricular-systolic stiffness, arterial load, left ventricular mass and elevated left ventricular end diastolic pressure, which might have adverse effects on LA because it was the transporting chamber conveying the blood into the left ventricle. Besides, all the patients enrolled in the study were paroxymal AF. Because most of AF was the disease originating from the LA, the differences of substrate properties in RA might not be as obvious as that in LA.

Renal Function and AF Recurrence After Catheter Ablation
In our study, the LA dimension, LA voltage and renal function groups were identified to be the independent predictors of an AF recurrence. The patients with a decreased GFR were associated with advanced atrial remodeling, including structural (enlarged LA size) and electrical (low LA voltage and prolonged activation time) changes, which were proved to result in a recurrence after AF ablation. One of the possible mechanisms for the association of the decreased GFR and abnormal LA substrate could be related to inflammation. Elevated levels of inflammatory markers, such as the C-reactive protein (CRP), interleukin-6 and fibrinogen, have been reported in renal insufficiency patients, even in its early stage. Our previous study has demonstrated that patients with a high CRP level were associated with an abnormal LA substrate and poor outcome after catheter ablation of AF. Therefore, the inflammatory process occurring from the early stage of renal dysfunction might result in atrial remodeling and a subsequent occurrence of AF and poor outcome after the catheter ablation.

Clinical Implications
Catheter ablation of AF provides an effective therapy for patients with symptomatic and drug-refractory AF, and its popularity continues to escalate. In addition to the equipment and strategies for AF ablation, identification and control of the risk factors might also play an important role in increasing the success rate of catheter ablation. Our study demonstrated that a decreased GFR had significant adverse effects on the prognosis after ablation. Therefore, in AF patients with renal insufficiency who undergo catheter ablation, it is important to prevent and retard the deterioration of the renal function by an aggressive control of the blood pressure, hyperglycemia and avoidance of nephrotoxic agents. However, further investigation is needed to determine whether the slowing down of the rapidity of the renal deterioration and improvement can improve the outcome of AF ablation.

Study Limitations
There were several limitations of the present study. First, 4-mm-tip non-irrigated catheters were used for ablations in some patients. However, there were no significant differences about the usage of non-irrigated catheters among the 3 groups (group 1 = 31.9%; group 2 = 34.7%; group 3 = 30.6%; P value = 0.866). Second, we hypothesized that inflammation could be the possible mechanism for the association of the decreased GFR and abnormal LA substrate. However, the speculation was based on the results of previous investigations, and inflammatory markers, such as CRP and interleukin-6, were not available in the present study. It deserves further prospective research to prove the hypothesis.

Conclusion
A decreased GFR was associated with an arrhythmogenic LA substrate and a higher recurrence rate of catheter ablation in patients with paroxysmal AF. The adverse effects of an impaired renal function on the atrial substrate occur from the early stage of a declining GFR. When managing patients with AF, renal function is an important issue that deserves more attention.

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Disclosures
None.

References