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Jing Zheng

The Quzhou Affiliated Hospital of Wenzhou Medical University, QuzhouPeoplès Hospital

De-ling Zu

The Quzhou Affiliated Hospital of Wenzhou Medical University, QuzhouPeoplès Hospital

Keyun Cheng

The Quzhou Affiliated Hospital of Wenzhou Medical University, QuzhouPeoplès Hospital

Yun-long Xia

The First Affiliated Hospital of Dalian Medical University, The First Affiliated Hospital of Dalian Medical University

Ying-xue Dong

The First Affiliated Hospital of Dalian Medical University, The First Affiliated Hospital of Dalian Medical University

Zhen-yan Gao (✉ gaozhenyan80@163.com)

The Quzhou Affiliated Hospital of Wenzhou Medical University, QuzhouPeoplès Hospital

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Decreased eGFR predicts long-term recurrence after catheter ablation of atrial fibrillation

Jing ZHENG¹, De-ling ZU¹, Ke-yun CHENG¹, Yun-long XIA², Ying-xue DONG², Zhen-yan GAO¹,

¹Department of Cardiology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People`s Hospital, Quzhou, Zhejiang, 324000, China

²Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, 116000, China

Correspondence: Ying-xue DONG² and Zhen-yan GAO¹, ²Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, 116000, China. Email: dlsusan@126.com; ¹Department of Cardiology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People`s Hospital, Quzhou, Zhejiang, 324000, China. Email: gaozhenyan80@163.com.

Background: Catheter ablation is an established therapy for atrial fibrillation (AF), but recurrence after ablation is still a great challenge. A higher prevalence of AF has been reported among patients with chronic renal disease. However, little is known about the effect of renal function on the efficiency of AF ablation. This study aimed to evaluate the effect of renal function on the prognosis of catheter ablation for AF.

Methods: A total of 306 consecutive drug-refractory symptomatic patients with AF who underwent first-time catheter ablation were enrolled in the present study. The individuals underwent circumferential pulmonary vein isolation for paroxysmal AF and stepwise ablation for persistent AF.

Results: Following up 27.2 ± 19.5 months after a single procedure, 202 patients (66.01%) were free of atrial tachyarrhythmia (non-recurrence group), and the other 104 patients experienced recurrence (recurrence group). The recurrence group had a larger left atrial diameter (LAD) and left atrial volume (LAV), a higher LAV index (LAVI) ($p < 0.01$, respectively), and a lower estimated glomerular filtration rate (eGFR) (53.5 ± 14.4 vs. 65.5 ± 13.3 ml/min/1.73², $p < 0.001$) and creatinine clearance rate (CCr) (85.2 ± 26.1 vs. 101.5 ± 29.4 ml/min, $p < 0.05$). Multivariate logistic analysis indicated eGFR and LAVI as independent predictors of long-term recurrence after single catheter ablation.

Conclusion: Decreased eGFR and elevated LAVI may facilitate the long-term recurrence of atrial tachyarrhythmia after catheter ablation for AF.

Key Words: estimated glomerular filtration rate; atrial fibrillation; catheter ablation; recurrence

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia that accounts for a significantly increased risk of stroke and all-cause mortality [1, 2, 3]. Catheter ablation has evolved over the past decade and has been demonstrated as an established therapy for paroxysmal AF and persistent AF [4]. However, recurrence after ablation is still a great challenge. There are several identical risk factors between AF and renal insufficiency, such as hypertension, diabetes mellitus, and age [5]. Additionally, a higher prevalence of AF has been reported among patients with different stages of chronic renal disease [6]. However, the effect of renal function on the efficiency of AF ablation has not been well elucidated. The present study aimed to assess the role of renal function in predicting long-term recurrence after catheter ablation of AF.

METHODS

Study Population The present study enrolled consecutive AF patients who underwent first-time catheter ablation between January 2008 and April 2013 in the First Affiliated Hospital of Dalian Medical University. The inclusion criteria were as follows: age between 18 and 80 years, symptomatic AF despite the use of at least one antiarrhythmic drug, prior attempts of electrical cardioversion, and severe adverse events on rhythm-control drugs. Exclusion criteria were defined as severe cardiac valvular diseases, left atrial diameter (LAD) >50 mm, left atrial thrombus, known bleeding diathesis, prior ablation for AF, and other severe comorbidities resulting in intolerance of perioperative antiarrhythmic/anticoagulation drugs. All patients signed an informed written consent form to the study protocol that was approved by Ethics committee of First Affiliated Hospital of Dalian Medical University.

Pre-procedure Management For paroxysmal AF, low-molecular-weight heparin was administered in the pre-procedure period. For persistent AF, effective anticoagulation therapy with warfarin was performed targeting an international normalized ratio (INR)

of 2 to 3 for more than 3 weeks. Warfarin was discontinued 5 days before the procedure and substituted with low-molecular-weight heparin (1.5 mg/kg twice daily). Moreover, antiarrhythmic agents, except amiodarone, were discontinued for at least 5 half-lives before the procedure. Renal function was evaluated by the estimated glomerular filtration rate (eGFR)[7] and creatinine clearance rate (CCr)[8] 1-2 days before the procedure. All patients underwent transthoracic echocardiography performed by two experienced senior cardiac sonographers. LAD was measured using two-dimensional anteroposterior linear dimensions obtained from the parasternal long-axis view [9]. Left atrial volume (LAV) was assessed offline with Simpson's method using apical four-chamber and apical two-chamber views at ventricular end-systole [9] and indexed to body surface area calculated by the DuBois formula [10]. CHADS₂ (congestive heart failure, hypertension, age \geq 75 years, type 2 diabetes, and previous stroke or transient ischaemic attack [doubled]) [11], CHA₂DS₂-VASc (congestive heart failure, hypertension, age \geq 75 years [doubled], type 2 diabetes, previous stroke, previous stroke or transient ischaemic attack [doubled], vascular disease, age 65 to 75 years, and sex category) [10] and R₂CHADS₂ (renal insufficiency [doubled], congestive heart failure, hypertension, age \geq 75 years, type 2 diabetes, and previous stroke or transient ischaemic attack [doubled]) [12] scores were calculated for each individual.

Electrophysiological Study and Catheter Ablation After exclusion of intracardiac thrombi by transesophageal echocardiography and assessment of pulmonary veins by CT scanning, CA was performed according to the HRS/EHRA/ECAS 2007 Consensus Statement on Catheter and Surgical Ablation of AF [13]. Briefly, under local anesthesia, after two trans-septal punctures, a mapping and ablation catheter and a circumferential mapping catheter were introduced into the left atrium. Radiofrequency energy was delivered at a power output of 30–40W and at a flow rate of 22 ml/min with a maximum temperature of 45 °C. Circumferential pulmonary vein isolation (CPVI) was performed by the 3D mapping system for paroxysmal AF. The end-point of CPVI was complete isolation of pulmonary vein potentials. Besides CPVI, further steps was performed for persistent AF, including roof line, mitral

isthmus line, and complex fractionated atrial electrograms for ablation, the so-called stepwise ablation. If AF or atrial tachycardia continued despite the wide ablation above, pharmacological/electrical cardioversion was performed afterwards.

Post-procedure Management After ablation, oral anticoagulation with warfarin was continued for at least 3 months, and subcutaneous low-molecular-weight heparin injections were discontinued after targeting INR. Amiodarone was administered to persistent AF patients routinely with oral doses of 600 mg/day for 1 week and 200 mg/day for 3 months after ablation.

Follow-up After discharge from the hospital, patients were followed up systematically at 1, 3, 6 and 12 months and then every 6 months in the outpatient department, including 24-hour Holter recording and 12-lead electrocardiogram. Patients were encouraged to report palpitations and any other symptoms suggestive of tachycardia outside follow-up visits. Recurrence was defined as atrial tachyarrhythmias sustained for more than 30 s beyond a blanking period of 3 months [13], including AF, atrial flutter or atrial tachycardia.

Statistical Analysis Results are presented as the mean \pm standard deviation for continuous variables and as frequency (percentages) for categorical variables. Group comparisons were performed using the t-test or χ^2 -test, as appropriate. Logistic regression analysis was used to identify the predictors for recurrence [15]. Receiver operating characteristic (ROC) curves were generated to compare and evaluate the value of the independent predictors of AF recurrence after ablation. All tests were two-sided, and $p < 0.05$ was considered to be significant. Statistical analysis was conducted using SPSS 7.0 and MedCalc 7.3.

RESULTS

Baseline characteristics and procedure data A total of 306 patients were enrolled in the present study: patients with persistent AF (n=120) underwent stepwise ablation, and patients with paroxysmal AF (n=186) underwent CPVI. The mean age was 56.7 ± 10.4 years. In total, 226 cases were male (73.9%). Following up 27.2 ± 19.5 months after a single procedure, 104 patients (34.0%) experienced recurring atrial

tachyarrhythmias (recurrence group), with 40.0% for persistent AF patients and 30.1% for paroxysmal AF patients. In addition, 202 patients maintained sinus rhythm without antiarrhythmic drugs (non-recurrence group). There were no differences in age, male sex, hypertension, diabetes mellitus, AF type, coronary heart disease, ischaemic stroke, CHADS₂, CHA₂DS₂-VASc and R₂CHADS₂ scores, or procedure data (procedural time, X-ray exposure time, ablation time) between the two groups (Table 1).

Echocardiographic characteristics Compared with the non-recurrence group, patients in the recurrence group had a higher LAD, LAV and LAVI (Table 2). Multivariate analysis suggested only LAVI as an independent predictor for long-term recurrence after AF ablation (Fig. 1). The ROC curve showed an area under the curve (AUC) of 0.708 (95% CI, 0.65 to 0.76, $p < 0.001$) for LAVI. A cut-off point of 30 ml/m² of the LAVI (Fig. 1, blue line) had a specificity of 71.8% and a sensitivity of 62.5%, with a positive/negative predictive value of 52.8%/79.2%. Increased LAVI contributed to higher recurrence (Fig. 2).

Renal insufficiency Univariable analysis showed that the patients in the recurrence group had a lower eGFR (53.5 ± 14.4 vs. 65.5 ± 13.3 ml/min/1.73², $p < 0.001$) and CCr (85.2 ± 26.1 vs. 101.5 ± 29.4 ml/min, $p < 0.05$) than those in the non-recurrence group (Table 3). Multivariable analysis indicated that eGFR was an independent risk factor for recurrence. The AUC of eGFR was calculated to be 0.725 (95% CI, 0.67 to 0.77, $p < 0.001$). The optimal cut-off point for eGFR (Fig. 1) as an independent predictor was 55 ml/min/1.73², with a specificity of 79.2% and a sensitivity of 51.9% and a positive/negative predictive value of 56.2%/76.2%. Patients with an eGFR ≤ 55 ml/min/1.73² had a significantly increased rate of recurrence (Fig. 2).

DISCUSSION

In the present study, a single ablation of AF was associated with a favourable outcome. Following up 27.2 ± 19.5 months, the overall recurrence rate was 34.0%, with 40.0% for persistent AF patients and 30.1% for paroxysmal AF patients. Multivariate logistic regression analysis indicated that pre-procedural LAVI and eGFR were independent

predictors of long-term recurrence. A higher LAVI and a lower eGFR contributed to long-term recurrence after a single procedure for AF.

CHADS₂, CHA₂DS₂-VASc, and R₂CHADS₂ score and AF Many factors have been proposed as predictors of prognosis after AF ablation, such as congestive heart failure, hypertension, diabetes, previous stroke and sex [14-17]. CHADS₂ and CHA₂DS₂-VASc scores, widely used to predict stroke risks among patients with AF, involve the abovementioned predictors. The R₂CHADS₂ score is a new stroke score that combines the CHADS₂ score and an index of renal insufficiency. Chen et al [18] demonstrated a positive relationship between new-onset AF incidence and CHADS₂ scores in a prospective cohort study among Taiwanese patients. Further studies identified a predictive value of CHADS₂, CHA₂DS₂-VASc and R₂CHADS₂ scores for post-ablation recurrence of AF [18,19,20]. Letsas KP et al. [21] reported that the predictive accuracy of both CHADS₂ and CHA₂DS₂-VASc was mediocre. Inconsistent with Kornej's and Chen's studies, the present study showed no significant differences in CHADS₂, CHA₂DS₂-VASc, or R₂CHADS₂ scores between the recurrence and non-recurrence groups. This finding may be partly ascribed to a rigorous inclusion. Patients with severe comorbidities were excluded.

Renal insufficiency and AF There is a higher prevalence of AF among patients with different stages of chronic renal disease [6]. CCr is widely used for the evaluation of renal failure in the clinic, while eGFR is preferred because it is more reliable, cheaper and easier to perform as a preoperative renal function test [22, 23, 24]. The R₂CHADS₂ score, involving an index of renal insufficiency determined as CCr, may not effectively evaluate the effect of renal function on the prognosis of AF ablation. The REGARDS study further demonstrated that the prevalence of AF gradually increased with a decreasing eGFR [25]. In the present study, eGFR was calculated as a renal function index instead of CCr, and multivariate logistic regression analysis showed that pre-procedure eGFR was an independent predictor of long-term recurrence. This confirmed that eGFR was superior to CCr as a prognostic index of AF ablation. Even mild renal insufficiency may have an unavoidable effect on recurrence after AF ablation.

Active sympathetic and renin-angiotensin-aldosterone systems (RAAS) play important roles in renal insufficiency [26, 27, 28], which also involves the pathogenesis of AF [29]. Norepinephrine released from sympathetic nerve endings enhances the Ca^{2+} transient, which may activate the $\text{Na}^{+}\text{-Ca}^{2+}$ exchange current and induce late phase 3 early afterdepolarization, resulting in focal discharge and AF [30, 31]. AngII and aldosterone were elevated in patients with renal insufficiency, and both could promote oxidative stress and atrial fibrosis, so-called atrial structural remodelling [32, 33]. Aldosterone also decreases the transient outward K^{+} current and I_{to} density secondary to the rise in Ca^{2+} current, which generates abbreviation of action potential, the so-called atrial electrical remodelling, and induces AF [34]. Another workable mechanism for eGFR influencing on AF recurrence may be inflammation. Patients with renal insufficiency, even in the early stage, have been reported to have high expression of inflammatory factors, such as hypersensitive C-reactive protein, interleukin-6 and fibrinogen [35, 36]. In the early stage of renal insufficiency, inflammation could induce myocardial remodelling, which might result in recurrence of atrial arrhythmias after catheter ablation. Lin et al [37] found that patients with higher hypersensitive C-reactive protein levels had lower mean bipolar peak voltage in the LA, suggesting extensive atrial remodelling, severe substrate and a greater possibility of non-pulmonary vein triggers. Meanwhile, these patients have a relatively higher mean dominant frequency value and widely-distributed AF nests in the LA. In addition, C-reactive protein may increase reactive oxygen species and enhance LA fibrosis, leading to atrial dilation and atrial dysfunction [38]. Therefore, the pathological mechanisms above may facilitate the recurrence of atrial tachyarrhythmia after AF ablation.

Left atrial remodelling and AF Water-sodium retention, hyperactive sympathetic tone and RAAS activation induced by renal insufficiency [26, 27, 28] increase left atrial volume overload and cause atrial remodelling. As reported in previously published studies, left atrial enlargement is the hallmark of atrial remodelling, which facilitates the prevalence of atrial arrhythmias, especially AF [39, 40]. With the enlargement of the atria, progressive changes in cellular ultrastructure and

extracellular matrix (composition and volume) develop. These abnormalities induce myocardial and interstitial fibrosis, local conduction heterogeneities and electrical dissociation between muscle bundles, consequently resulting in the initiation and perpetuation of AF [39, 41]. The persistence of atrial remodelling, potentially explaining arrhythmogenic substrates, is incremental to the post-procedure recurrence of AF [42, 43].

Hui-Ling Lee et al [44] confirmed a larger LAD was demonstrated to increase the probability of AF recurrence after surgery significantly by a three-year longitudinal study. Despite its procurability, its validity has recently been challenged, as the LA is an asymmetrical cavity. Conversely, biplane LAV provides an overall and reproducible estimation of left atrial size when compared with reference standards such as magnetic resonance imaging. Considering the individual differences, LAVI, calculated as LAV indexed to body surface area, is more comparable in accuracy and reproducibility. Procolo Marchese et al [45] proved that LAVI was a more exact estimate of LA remodelling than LAD. LAVI was strongly associated with the risk of AF recurrence after cardioversion, with a cut-off of 31 ml/m². Kataoka T et al [46] demonstrated LAVI in predicting failure of the surgical maze procedure for AF patients. However, the role of LAVI in the prognosis of AF ablation has not been identified.

In the present study, we also found that LAD, LAV and LAVI were higher in the recurrence group. Multivariable analysis proved that LAVI, rather than LAV and LAD, was an independent predictor for long-term prognosis after catheter ablation of AF. Increased LAVI contributed to long-term recurrence, with an optimal cut-off of 30 ml/m². This result indicated that LAVI, characterized as left atrial remodelling, may be an important determinant for the prognosis of AF ablation.

Clinical implications Recurrence after AF ablation has remained a puzzle for both doctors and patients. Evaluation of the risk factors for recurrence is crucial in boosting the success rate. The present study demonstrated that a decreased eGFR and an increased LAVI had significant adverse effects on the long-term prognosis after a single procedure. Therefore, the preprocedural eGFR and LAVI might be taken into

consideration for optimal patient enrolment for AF ablation. Furthermore, it may be prudent to perform catheter ablation for patients with $eGFR \leq 55 \text{ ml/min/1.73}^2$ or $LAVI \geq 30 \text{ ml/m}^2$.

Limitations There were several limitations in the present study. First, the mean eGFR of the patients in the present study was $61.4 \pm 14.8 \text{ ml/min/1.73}^2$, and severe renal insufficiency was excluded. The current data were inadequate to fully evaluate renal function in the prognosis of AF ablation. Second, there was a lack of laboratory indicators for further study of the mechanism, such as inflammatory markers and left atrial voltage. Third, limited by follow-up means, AF recurrence rates may be underestimated by ignoring asymptomatic paroxysmal AF. Mobile health technology may improve the comprehensive management of atrial fibrillation [47]. Further investigation is needed to determine whether improving renal insufficiency can enhance the long-term success of catheter ablation for AF.

CONCLUSIONS

The present study showed that decreased eGFR and elevated LAVI contribute to increased recurrence after AF ablation. Renal insufficiency and LA remodelling might be important determinants for the long-term prognosis of AF, ablation and should be considered for optimal AF patient selection for catheter ablation.

DECLARATIONS

Ethics approval and consent to participate: This study protocol for involving human data was in accordance with the Declaration of Helsinki, and was approved by Ethics committee of First Affiliated Hospital of Dalian Medical University (Ethics Reference NO: YJ-KY-FB-2013-50). Design and implementation of this study followed the HRS/EHRA/ECAS 2007 Consensus Statement on Catheter and Surgical Ablation of AF (<http://doi.org/10.1016/j.hrthm.2007.04.005>), including indications, surgical procedures, and drug treatment regimens. All patients signed an informed written consent form.

Consent for publication: Written informed consent for publication was obtained from

all participants.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: None.

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Authors' contributions: Z.G, Y.D and Y.X guided the design of conceptualization and methodology, furthermore Z.G was responsibility for the research activity planning and execution. J.Z wrote the original manuscript text. J.Z, D.Z and K.C finished the data collation. J.Z and D.Z prepared tables 1-3. J.Z and K.C prepared figures 1-2. Z.G and Y.D were responsible for manuscript review and editing. All authors reviewed the manuscript.

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ABBREVIATIONS

AF= atrial fibrillation

LA= left atrium

LAD= left atrial diameter

LAV=left atrial volume

LAVI=left atrial volume index

INR= international normalized ratio

eGFR=estimated glomerular filtration rate

CCr=creatinine clearance rate

CPVI =circumferential pulmonary vein isolation

ROC=receiver operating characteristic

AUC= area under the curve

RAAS= renin-angiotensin-aldosterone systems

Table 1	Baseline characteristics and procedure data between recurrence and non-recurrence groups		
Variable	Recurrence Group (n=104)	Non-recurrence Group (n=202)	P Value
Age (years)	57.0±10.9	56.6±10.1	0.464
Sex (M/F)	73/31	153/49	0.295
History of AF (years)	3.0±1.5	2.6±2.3	0.848
Persistent AF (%)	48 (46.2%)	72 (35.6%)	0.065
Hypertension (n)	46 (44.2%)	83 (41.1%)	0.598
Diabetes mellitus (n)	6 (5.8%)	23 (11.4%)	0.112
Coronary heart disease (n)	9 (8.7%)	22(10.9%)	0.539
Ischaemic stroke (n)	8 (7.7%)	12(5.9%)	0.557
CHADS ₂ score	0.8±1.0	0.8±0.9	0.946
CHA ₂ DS ₂ -VASc score	1.3±1.2	1.2±1.2	0.599
R ₂ CHADS ₂ score	1.6±1.4	1.4±1.3	0.082
Produce time (h)	2.5±1.5	2.3±1.3	0.265
Exposure time (s)	61.6±29.3	63.3±27.9	0.176
Ablation time (min)	53.8±17.4	55.6±19.9	0.198

Table 2	Echocardiographic characteristics and renal function between recurrence and non-recurrence groups		
Variable	Recurrence Group (n=104)	Non-recurrence Group (n=202)	P Value
LAD (mm)	41.6±5.0	39.39±3.43	<0.001
LAV (ml)	58.6±17.7	50.5±11.6	<0.001
LAVI (ml/m ²)	33.7±9.7	27.1±6.5	<0.001
LVEF (%)	57.2±5.7	59.9±4.8	0.108

Table 3	Renal function between recurrence and non-recurrence groups		
Variable	Recurrence Group (n=104)	Non-recurrence Group (n=202)	P Value
eGFR (ml/min/1.73 ²)	53.5±14.4	65.5±13.3	<0.001
CCr (ml/min)	85.2 ± 26.1	101.5 ± 29.4	0.033

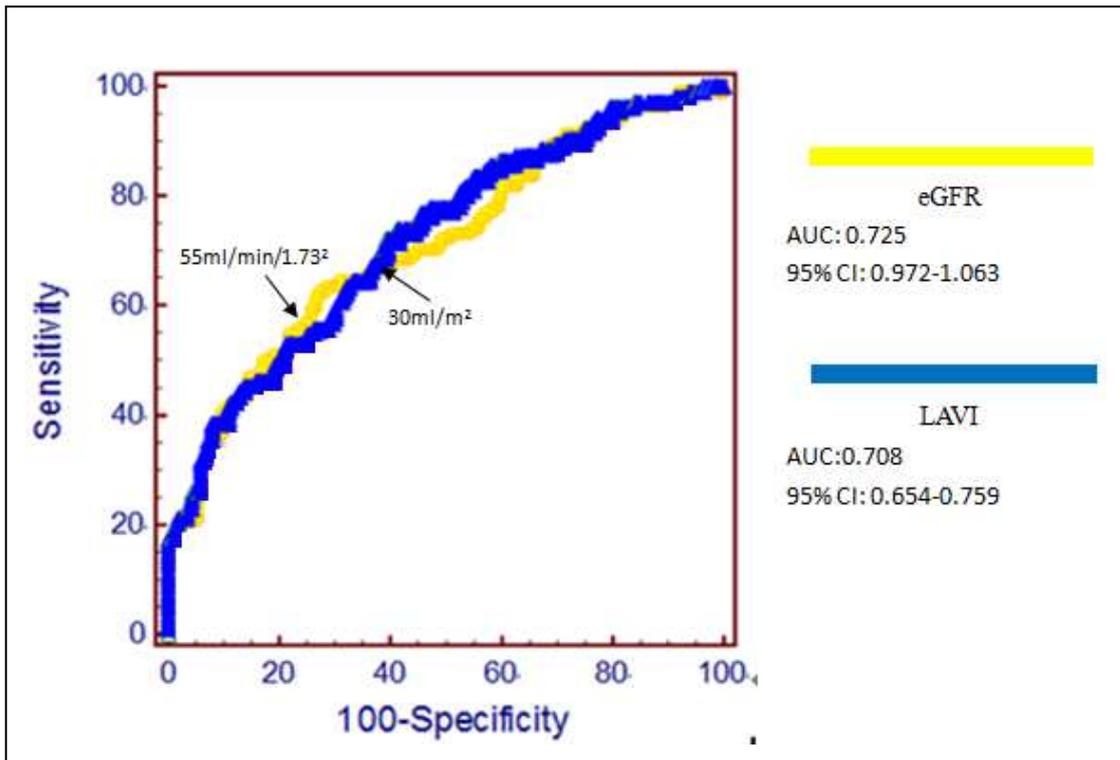


Figure 1. LAV, LAVI, eGFR and AF recurrence

The ROC curve analysis of the eGFR (yellow line) and LAVI (blue line) according to recurrence of AF after a single ablation procedure. Arrows indicate optimal cut-off point for sensitivity and specificity.

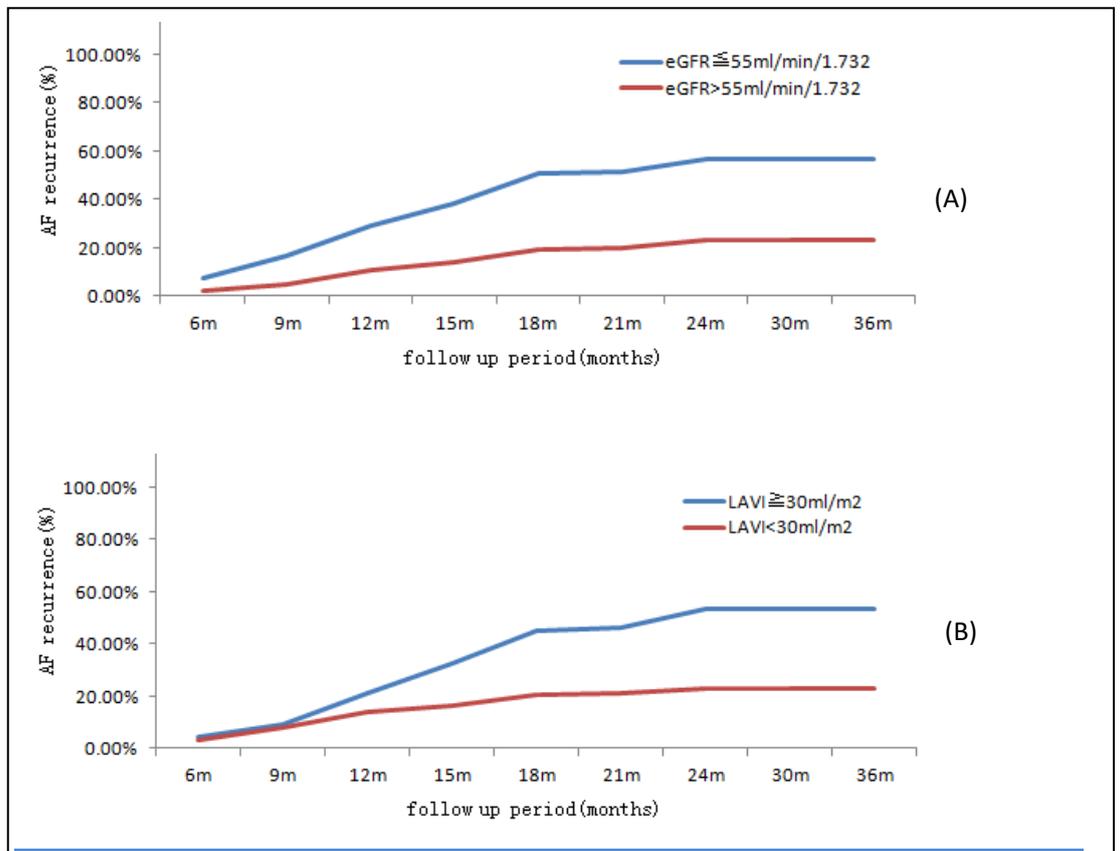


Figure 2 Long-term AF recurrence after a single catheter ablation

(A) The long-term recurrence in patients with or without $eGFR \leq 55 \text{ ml/min/1.73}^2$.
 (B) The long-term recurrence in patients with or without $LAVI \geq 30 \text{ ml/m}^2$.