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Z.-H. Lu · N. Liu · R. Bai · Y. Yao · S.-N. Li · R.-H. Yu · C.-H. Sang · R.-B. Tang · D.-Y. Long · X. Du · J.-Z. Dong · C.-S. Ma
Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing

HbA1c levels as predictors of ablation outcome in type 2 diabetes mellitus and paroxysmal atrial fibrillation

Paroxysmal atrial fibrillation (PAF) is the most common arrhythmia, and a large number of patients with AF have no detectable heart disease. Previous epidemiological studies assessed the relationship between type 2 diabetes mellitus (T2DM) and the subsequent risk of AF, and reported that DM was an independent risk factor for AF [1]. A recent meta-analysis of 108,703 cases of AF in 1,686,097 patients from seven prospective cohort and four case-controlled studies found that DM was associated with an overall 34% increased risk of AF after correcting for the presence of publication bias [2]. In patients with T2DM, radiofrequency catheter ablation (RFCA) of symptomatic and drug-refractory AF provides significant clinical benefits over antiarrhythmic drugs, and appears to be a reasonable approach in terms of feasibility, effectiveness, and low procedural risk [3]. Because the recurrence of AF after RFCA is common, ranging from 20 to 60% [4], it is important to identify risk factors for AF recurrence after RFCA.

Glycated hemoglobin A1c (HbA1c) is a well-established biomarker that is recommended for the diagnosis of DM, and is widely used for assessing the glycemic status of diabetic patients. The UK Prospective Diabetes Study Group (UKPDS), a long-term prospective study, confirmed that DM complications are directly related to the integrated mean glucose concentration, which is reflected by HbA1c [5]. Epidemiological studies revealed that high levels of HbA1c were strongly associated with microvascular diabetic complications, cardiovascular disease, and all-cause mortality in patients with DM [6]. In addition, high levels of HbA1c were independently associated with the prevalence of AF [7]. However, it remains unknown whether HbA1c levels affect the outcome of RFCA. The aim of this study was to evaluate whether HbA1c levels could predict procedural outcome in patients with T2DM and PAF undergoing ablation.

Patients and methods

Study subjects

A total of 149 consecutive patients undergoing their first procedure with drug-refractory symptomatic PAF combined with T2DM were enrolled in this study between June 2010 and June 2013 at Beijing An Zhen Hospital (attached to Capital Medical University, Beijing, China). All patients gave written informed consent, and the study was approved by the Institutional Review Board.

Definitions

The diagnostic criteria of T2DM were a fasting plasma glucose level of ≥7.0 mmol/l, a 2-h plasma glucose level in a 75-g oral glucose tolerance test (OGTT) of ≥11.1 mmol/l, or a random plasma glucose level of ≥11.1 mmol/l. A confirmatory repeated laboratory test (fasting plasma glucose or a 2-h plasma glucose in a 75 g OGTT) was performed on another day in patients without symptomatic hyperglycemia [8]. PAF was defined as an AF episode that lasted less than 7 days and spontaneously terminated. $CHADS_2$ scores were calculated for cardiac failure, hypertension, age ≥75 years, diabetes mellitus, and stroke (doubled) [9]. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Biochemical measurements

Peripheral venous blood samples were collected after an overnight fast on the morning of admission. High-performance liquid chromatography was used to measure HbA1c levels (Bio-Rad Variant II TURBO HbA1c analyzer, USA). FPG was measured using the glucose oxidase peroxidase method (Beckman 5400 automatic biochemistry analyzer, USA).

Electrophysiological study

All antiarrhythmic medications, with the exception of amiodarone, were discontinued for at least five half-lives. The presence of intracardiac thrombus was excluded with transesophageal echocardiography before the catheter ablation procedure. Vascular access was obtained via the bilateral femoral veins. A decapolar catheter was positioned in the coronary sinus to record electrograms. Intravenous heparin was administered to maintain an activated clotting time of 300–350 s after transeptal catheterization. A 3.5-mm tip saline-irrigated catheter (Thermocool, Biosense-Webster) was used for mapping and ablation. A three-dimensional reconstruction of the left atrium and pulmonary veins

Tab. 1 Characteristics of the recurrence-free and recurrence patients

	Recurrence-free group (n=89)	Recurrence group (n=60)	p
Age, years	61±8	63±9	0.141
Male, %	62.9	50	0.117
Body mass index, kg/m^2	26.2±3.0	27.2±3.3	0.043
AF duration, years	4.1±5.0	6.4±7.1	0.033
Left atrial size on echo, mm	37.9±4.5	41.0±5.3	0.000
End-diastolic LV dimension, mm	47.2±5.0	48.1±4.0	0.218
Left ventricular posterior wall thickness, mm	9.2±1.1	9.1±1.3	0.905
Interventricular septal thickness, mm	9.1±1.2	9.3±1.3	0.252
Left ventricular ejection fraction, %	65.7±5.7	64.0±7.6	0.109
Left ventricular diastolic dysfunction, %	24.7	25.0	0.969
Hypertension, %	61.8	61.7	0.987
Hypertension duration, years	6.9±8.4	7.8±10.0	0.578
Systolic blood pressure, mmHg	125.0±10.7	125.1±8.0	0.974
Diastolic blood pressure, mmHg	75.2±11.3	76.7±7.9	0.367
Diabetes mellitus, years	5.5±5.0	6.7±5.9	0.189
Coronary artery disease, %	16.9	20.0	0.625
Prior stroke/TIA, %	6.7	11.7	0.296
Smoking, %	28.1	33.3	0.494
$CHADS_2$ score	1.8±0.8	1.9±0.9	0.417
Oral hypoglycemic agents, %	74.2	73.3	0.911
HbA1c, %	6.8±1.1	7.2±1.0	0.032
Fasting plasma glucose, mmol/l	7.0±1.8	7.0±2.0	0.984

Tab. 2 Multivariate analyses of atrial tachyarrhythmia recurrence after first ablation

	p	HR	95% CI
Left atrial size	0.000	1.109	1.051–1.170
HbA1c	0.034	1.222	1.016–1.471

and a circumferential ablation to isolate the left and right pulmonary veins in pairs was performed under the guidance of an electroanatomic mapping system (CARTO 3 system, Biosense Webster). Radiofrequency energy (maximum power, 35 W; target temperature, 43°C; infusion rate, 17 ml/min) was delivered for 30–60 s at each point until either the maximal local electrogram amplitude was decreased by at least 80%, or double potentials were observed. A decapolar ring catheter (Lasso, Biosense Webster) was used to verify pulmonary vein isolation, which was characterized by the dissociation of pulmonary vein potential from the left atrial activity or the elimination of residual potential inside the circumferential ablation lines. Patients were treated with an antiarrhythmic drug and warfarin for 3 months after catheter ablation. All patients were treated with an anticoagulant (warfarin) to maintain an international normalized ratio of 2.0–3.0. Anticoagulation was discontinued after the 3-month follow-up according to the $CHADS_2$ score.

Follow-up

All patients were followed up in the outpatient clinic, with 12-lead electrocardiography and 24-h Holter monitoring performed 1, 3, 6, 9, and 12 months after the catheter ablation procedure, and then every 3 months thereafter. In addition, telephone interviews were conducted monthly for all patients. An additional electrocardiogram and 24-h Holter monitoring were obtained promptly if patients had any arrhythmia-related symptoms. The first 3 months after ablation was defined as the blanking period. Any episode of symptomatic or asymptomatic atrial tachyarrhythmias (including AF, atrial flutter, and atrial tachycardia) with Holter monitoring or electrocardiography that lasted over 30 s more than 3 months after the ablation was considered as arrhythmia recurrence.

Statistical analysis

Continuous variables are expressed as means ± SD, and were compared using an independent samples t test after checking for equality of variances using Levene's test. Categorical variables were compared using chi-squared tests. Cox proportional hazards regression analysis was performed to identify risk factors for recurrence. The arrhythmia-free survival curves for both groups were presented as Kaplan–Meier plots and were compared using log-rank tests. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, Ill.).

Results

Characteristics of the recurrence-free and recurrence groups

A total of 149 patients with PAF and T2DM undergoing catheter ablation were enrolled in the study. Of these, 60 (40.3%) developed recurrence after a median 12-month (range, 3–41 months) follow-up. The characteristics of the patients in the recurrence-free and recurrence groups are listed in **Tab. 1**. Antihypertensive drugs were similar for hypertensive patients in the recurrence group and the recurrence-free group: an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB; 67.6% vs. 58.2%, p=0.363), combination of an ACE inhibitor or an ARB and a calcium channel blocker (CCB; 24.3% vs. 29.1%, p=0.614), a CCB (8.1% vs. 12.7%, p=0.722).

Compared with the recurrence-free group, patients in the recurrence group presented with a greater BMI (27.2±3.3 vs. 26.2±3.0 kg/m^2, p<0.05), longer AF duration (6.4±7.1 vs. 4.1±5.0 years, p<0.05), larger left atrial size (41.0±5.3 vs. 37.9±4.5 mm, p<0.05), and higher HbA1c levels (7.2±1.0% vs. 6.8±1.1%, p<0.05). In addition, multivariate Cox regression analysis revealed that left atrium size [hazard ratio (HR) 1.109, 95% confidence interval (CI) 1.051–1.170, p=0.000] and HbA1c

(HR 1.222, 95% CI 1.016–1.471, p=0.034) were independent predictors of recurrent atrial tachyarrhythmia (**Tab. 2**).

HbA1c levels and recurrence

Receiver operating characteristic (ROC) analysis revealed that an HbA1c cut-off of ≥6.9% predicted recurrence with 55.0% sensitivity and 67.4% specificity (AUC =0.634, **Fig. 1**). Characteristics were similarly found in the HbA1c <6.9% and ≥6.9% groups (**Tab. 3**). Antihypertensive drugs were similar for hypertensive patients in the HbA1c ≥6.9% group and the HbA1c <6.9% group: an ACE inhibitor or an ARB (64.3% vs. 60.0%, p=0.673), combination of an ACE inhibitor or an ARB and a CCB (23.8% vs. 30.0%, p=0.506), a CCB (11.9% vs. 10.0%, p=1.000). Kaplan–Meier analysis demonstrated that 69.0% of patients in the HbA1c <6.9% group were arrhythmia-free at the end of the follow-up period compared with 46.8% of patients in the HbA1c ≥6.9% group (log-rank p=0.004, **Fig. 2**).

Left atrial size and recurrence

ROC analysis demonstrated that a left atrial size cut-off value of ≥39.0 mm predicted recurrence with 70.0% sensitivity and 55.1% specificity (AUC =0.672, **Fig. 1**). All patients were then further divided into four groups (A, B, C, and D) based on the combined indicators of HbA1c and left atrial size (**Fig. 3**). Group A included patients with an HbA1c of <6.9% and a left atrial size of <39.0 mm; 23.7% of patients (n=38) developed recurrence. Group B included patients with an HbA1c of <6.9% and a left atrial size ≥39.0 mm; 36.7% of patients (n=49) developed recurrence. Group C included patients with an HbA1c of ≥6.9% and a left atrial size of <39.0 mm; 31.0% of patients (n=29) developed recurrence. Group D patients exhibited an HbA1c ≥6.9% and a left atrial size of ≥39.0 mm; 72.7% of patients (n=33) developed recurrence.

Procedural outcome and complications

There were no significant differences in procedural or fluoroscopy times between the HbA1c <6.9% and ≥6.9% groups (**Tab. 3**). No procedural complications were observed in any patients.

Abstract · Zusammenfassung

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HbA1c levels as predictors of ablation outcome in type 2 diabetes mellitus and paroxysmal atrial fibrillation

Abstract

Aims. The aim of this study was to evaluate whether the levels of HbA1c could predict the outcome of ablation in patients with type 2 diabetes mellitus (T2DM) and paroxysmal atrial fibrillation (PAF).

Patients and methods. The study comprised 149 consecutive patients with T2DM and PAF who underwent their first circumferential pulmonary vein isolation. HbA1c levels were measured before ablation. Cox proportional hazards models were constructed to assess the relationship between HbA1c levels and the recurrence of atrial fibrillation (AF).

Results. Of the 149 patients, 60 (40.3%) developed AF recurrence after a median 12-month follow-up. Multivariate Cox regression analysis revealed that left atrium size and HbA1c were independent predictors of recurrent atrial tachyarrhythmia. Receiver operating characteristic analysis demonstrated that an HbA1c cut-off value of ≥6.9% predicted recurrence with 55.0% sensitivity and 67.4% specificity (AUC =0.634). The success rate of ablation was 69.0% in patients with an HbA1c value of <6.9% compared with 46.8% in those with an HbA1c value of ≥6.9% (log-rank test, p=0.004).

Conclusion. High levels of HbA1c were associated with an increased risk of recurrence of atrial tachyarrhythmia in patients with T2DM and PAF undergoing catheter ablation.

Keywords

Atrial fibrillation · Diabetes mellitus · Glycated hemoglobin · Catheter ablation · Outcome

HbA1c-Wert als Prädiktor für das Ergebnis der Ablation bei Diabetes mellitus Typ 2 und paroxysmalem Vorhofflimmern

Zusammenfassung

Ziel. Ziel der vorliegenden Studie war zu untersuchen, ob der HbA1c-Wert das Ergebnis der Ablation bei Patienten mit Diabetes mellitus Typ 2 (T2DM) und paroxysmalem Vorhofflimmern (PAF) prognostizieren konnte.

Patienten und Methoden. In die Studie aufgenommen wurden 149 konsekutive Patienten mit T2DM und PAF, bei denen erstmals eine zirkumferenzielle Pulmonalvenenisolation erfolgte. Vor Ablation wurde der HbA1c-Wert bestimmt. Um den Zusammenhang zwischen HbA1c-Wert und einem Rezidiv des Vorhofflimmerns (AF) zu erfassen, wurden Proportional-Hazard-Modelle nach Cox erstellt.

Ergebnisse. Bei 60 (40,3%) der 149 Patienten trat nach einer durchschnittlichen Nachbeobachtungsdauer von 12 Monaten ein VF-Rezidiv auf. Die multivariate Cox-Regressionsanalyse ergab, dass die Größe des linken Vorhofs und der HbA1c-Wert unabhängige Prädiktoren einer rezidivierenden Vorhoftachyarrhythmie waren. Die Receiver-operating-characteristics-Analyse zeigte, dass ein HbA1c-Grenzwert ≥6,9% ein Rezidiv mit einer Sensitivität von 55,0% und einer Spezifität von 67,4% (Fläche unter der Kurve, AUC =0,634) prognostizierte. Die Erfolgsrate der Ablation betrug 69,0% bei Patienten mit einem HbA1c <6,9% gegenüber 46,8% bei Patienten mit einem HbA1c ≥6,9% (Log-Rank-Test, p=0,004).

Schlussfolgerung. Hohe HbA1c-Werte gingen bei Patienten mit T2DM und PAF, bei denen eine Katheterablation erfolgte, mit einem erhöhten Rezidivrisiko für eine Vorhoftachyarrhythmie einher.

Schlüsselwörter

Vorhofflimmern · Diabetes mellitus · Glykiertes Hämoglobin · Katheterablation · Ergebnis

Discussion

T2DM is commonly accompanied by PAF. Previous community studies reported the presence of DM in 13% of patients with AF [10]. A multicenter study indicated that AF is relatively common

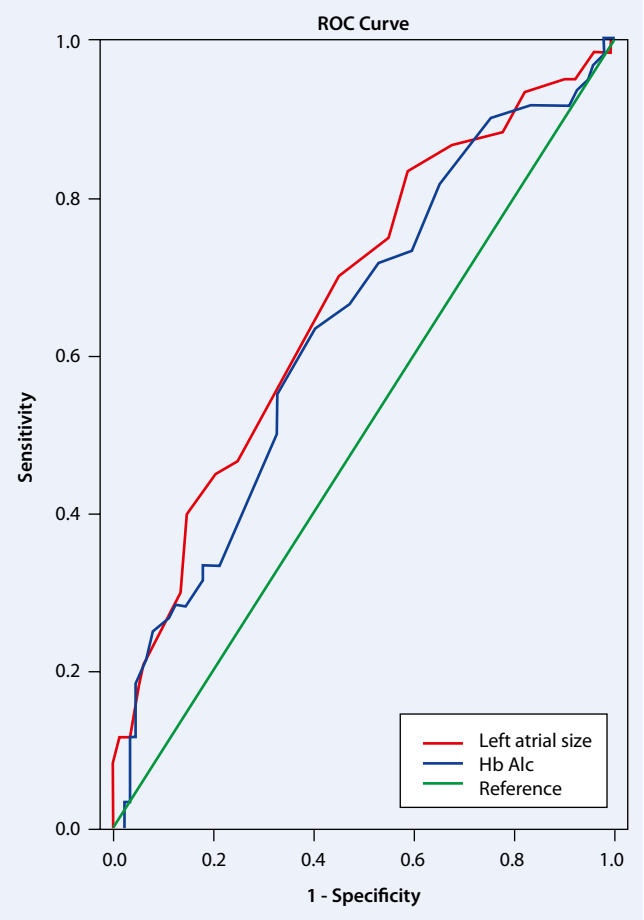

Fig. 1 ◀ Receiver operating characteristic (*ROC*) curve of HbA1c and left atrial size for predicting recurrence

in patients with T2DM, and demonstrated that there is a substantially higher risk of stroke, heart failure, cardiovascular death, and all-cause mortality in patients with coexistent T2DM and AF [11]. In patients with T2DM and PAF, catheter ablation provides significant clinical benefits over antiarrhythmic drug-based therapy. Ablation could be the first-line therapy for patients who do not respond to one or more class I or III antiarrhythmic drugs after symptomatic episodes of PAF [12]. Currently, circumferential ablation of the pulmonary veins is a central strategy for PAF, mainly by isolating the pulmonary vein ectopic electrical triggers that are important for the initiation of AF. Although elimination of the pulmonary vein triggers appears to be a reasonable approach that has low procedural risk and a success rate of ~77% over 12 months for PAF, recurrent atrial tachyarrhythmia is common, and can be observed in some patients because the underlying mechanisms that contribute to AF are multifactorial and complex [13].

The current study revealed that 40.3% of patients with PAF and T2DM undergoing catheter ablation develop recurrence after a median 12-month follow-up. The levels of HbA1c were higher in recurrent patients than in those who remained arrhythmia free. In diabetic patients with an HbA1c of ≥6.9%, the sinus rhythm maintenance rate was 46.8%, which is lower than that of diabetic patients with an HbA1c of <6.9% (69.0%). In addition, a higher HbA1c level was associated with an increased risk of recurrence of atrial tachyarrhythmias in patients with T2DM and PAF undergoing catheter ablation. This effect was independent of other risk factors for recurrence.

Glycosylated hemoglobin is formed by the exposure of hemoglobin to plasma glucose in a non-enzymatic reaction [14]. HbA1c is thought to reflect the mean plasma glucose over the previous 2–3 months. Because HbA1c can be measured at any time and is not associated with day-to-day variability, it is more convenient, stable, and accurate than fasting plasma glucose or 2-h plasma glucose levels in a 75-g OGTT [15]. HbA1c was introduced as a parameter for diagnosing diabetes by the American Diabetes Association in 2010. It is considered to be the gold standard for assessing the glycemic and metabolic control of DM.

HbA1c is also a better predictor of cardiovascular events than fasting plasma glucose or 2-h plasma glucose levels. Our study showed that a higher HbA1C level was accompanied by a higher incidence of hypertension and coronary artery disease despite no statistically significant difference, which was in line with epidemiological studies [6]. A positive linear association was observed between HbA1c and the risk of AF in both patients with and without DM. With every 1% increase in HbA1c, the risk of AF increased by 5% in patients without DM and by 13% in patients with DM [16]. This suggests that HbA1c levels and poor glycemic control are independently associated with an increased risk of AF, although the underlying mechanism governing this relationship is unclear.

In the current study, HbA1c levels, but not fasting plasma glucose, was higher in the recurrence group. Multivariate Cox regression analysis found that HbA1c levels were associated with the risk of AF recurrence, with a hazard ratio of 1.222. Therefore, for every 1% increase in HbA1c, the risk of AF recurrence increased by 22.2%. This suggests that abnormal glucose metabolism, and particularly long-term hyperglycemia over the previous 2–3 months, may contribute to arrhythmia recurrences and be associated with a worse prognosis. Abnormal glucose metabolism could increase atrial arrhythmogenicity, and lead to a longer intra-atrial activation time and lower atrial voltage than normal glucose metabolism [17]. The low-voltage area of the atrium could aggravate an interatrial conduction delay, which results in the formation of reentry circuits and promotes the progression of AF [18].

Late DM complications can occur on both small and large blood vessels, nerves, and the basal membranes of different tissues because of the consequences of long-term hyperglycemia [19]. Hyperglycemia plays an important role in the activation of

Tab. 3 Characteristics of patients with different HbA1c levels

	HbA1c <6.9% (*n*=87)	HbA1c ≥6.9% (*n*=62)	*p*
Age, years	62±8	62±9	0.673
Male, %	60.9	53.2	0.349
BMI, kg/m^2	26.2±3.3	27.1±2.9	0.089
AF duration, years	5.4±6.3	4.6±5.6	0.436
Left atrial size on echo, mm	39.0±4.8	39.3±5.4	0.748
End-diastolic LV dimension, mm	47.7±4.3	47.4±5.2	0.643
Left ventricular posterior wall thickness, mm	9.1±1.2	9.2±1.2	0.733
Interventricular septal thickness, mm	9.1±1.2	9.3±1.3	0.458
Left ventricular ejection fraction, %	65.3±5.8	64.6±7.6	0.579
Left ventricular diastolic dysfunction, %	24.1	25.8	0.816
Hypertension, %	57.5	67.7	0.204
Hypertension duration, years	7.1±8.9	7.4±9.3	0.835
Systolic blood pressure, mmHg	125.5±10.9	124.3±7.6	0.443
Diastolic blood pressure, mmHg	75.5±12.0	76.1±6.7	0.717
Diabetes mellitus, years	5.4±4.7	6.8±6.2	0.154
Coronary artery disease, %	14.9	22.6	0.233
Prior stroke/TIA, %	6.9	11.3	0.215
Smoking, %	27.6	33.9	0.410
$CHADS_2$ score	1.7±0.8	2.0±0.9	0.094
Oral hypoglycemic agents, %	75.9	71.0	0.503
Procedure time, min	87.0±8.7	87.2±8.9	0.844
Fluoroscopy duration, min	18.7±4.0	18.2±3.7	0.430

oxidative stress and the overproduction of mitochondrial superoxide, which results in atrial ischemia and injury by triggering various metabolic pathways [20]. Hyperglycemia caused atrial electrical remodeling, structural remodeling, and a vulnerability to AF in diabetic rabbits owing to its role in atrial interstitial fibrosis and ionic remodeling [21].

HbA1c is also a target for intracellular glycoxidation and peroxidation reactions that result in the formation of advanced glycation end products (AGEs) [22]. A previous study reported that the levels of AGEs were positively correlated with AF, suggesting that AGEs might play an important role in the development of AF [23]. AGE accumulation after excessive cross-linking might participate in atrial structural remodeling by affecting the physiological properties of proteins in the extracellular matrix, which could result in tissue fibrosis, stiffening, and the loss of elasticity [24]. Atrial fibrosis is an important mechanism for atrial structural and electrical remodeling. Widespread atrial fibrotic deposits might result in conduction heterogeneity and thus contribute to the formation of a reentrant loop and change the forward propagation of fibrillatory wavelets, which causes atrial complex fragmentation potentials and delayed conduction [25].

The aim of the HbA1c cut-off value of <6.9% in the current study is similar to that of the HbA1c target of <7% recommended in the DCCT and UKPDS cohorts [26]. Glycemic control might play an important role in reducing the recurrence of atrial tachyarrhythmias. This is because the RFCA of PAF was a selective operation, and a history of AF was not an independent predictor of recurrent atrial tachyarrhythmia in the current study. AF ablation is a cost-comparable strategy. The estimated median total treatment cost using catheter ablation ranged from $ 16,278 to $ 21,294 in Canada [27]. Therefore, it is very important to minimize the recurrence rate of AF from an economic perspective. The current study provides novel valuable evidence to optimize the management strategy of diabetic patients with PAF after RFCA, and also improve the long-term cost effects of RFCA by achieving glycemic control.

This study also revealed that left atrial size is another independent risk factor for recurrence, consistent with previous studies [28]. Increased left atrial size might result from insulin resistance [29]. The atrial substrate plays an important role in the maintenance of AF and recurrence of atrial tachyarrhythmias. Enlargement of the left atrium could contribute to atrial heterogeneity and allow the propagation and development of reentrant electrical circuits. The current study revealed that a higher rate of AF recurrence in patients with HbA1c of ≥6.9% and a left atrial size of ≥39.0 mm compared with those with HbA1c of ≥6.9% or a left atrial size of ≥39.0 mm.

Study limitations

There are several limitations associated with the present study. First, follow-up was based on ECG-documentation or 24-h Holter recording, together with additional symptom-based detection of arrhythmia recurrences. Thus, additional asymptomatic arrhythmia recurrences may be overlooked. Second, the results of this study were non-randomized controlled trial data; therefore, there is some risk of bias. As such, additional multicenter randomized trials are required. Third, the median follow-up period of 12 months might be not long enough. Fourth, our study lacked HbA1c levels during follow-up. In the future, we aim to perform a prospective study with a greater sample size including metabolic syndrome as a single parameter and HbA1c levels during follow-up in the regression model.

Conclusion

In this study, we found that HbA1c and left atrium size were independent predictors of recurrent atrial tachyarrhythmia in patients with T2DM and PAF undergoing catheter ablation. HbA1c levels of ≥6.9% were associated with a lower procedural success rate. These results suggest that HbA1c levels are clinically important risk factors that are associated with AF recurrence. Combined indicators of HbA1c and left atrial size can further improve the prediction of AF recurrence after RFCA. The underlying mechanism

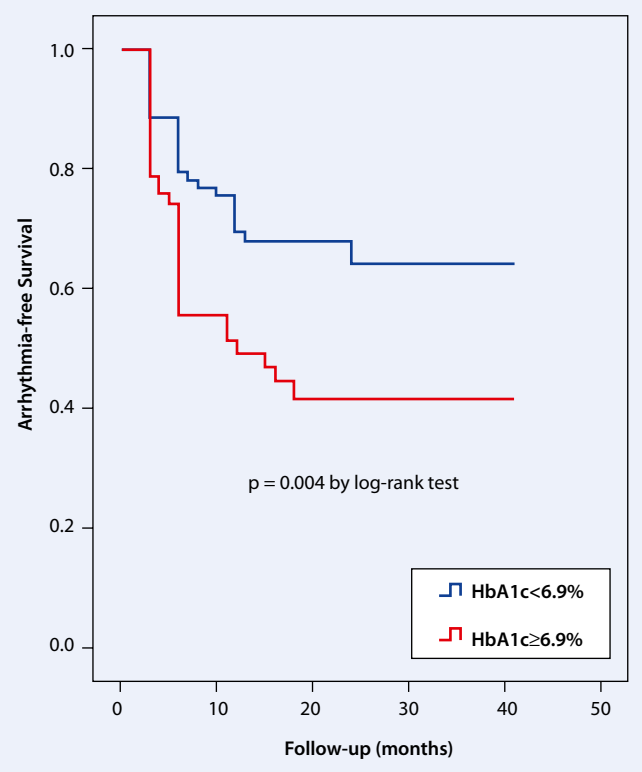

Fig. 2 ▲ Kaplan–Meier curves of freedom from recurrent atrial tachyarrhythmias in the HbA1c <6.9% and ≥6.9% groups

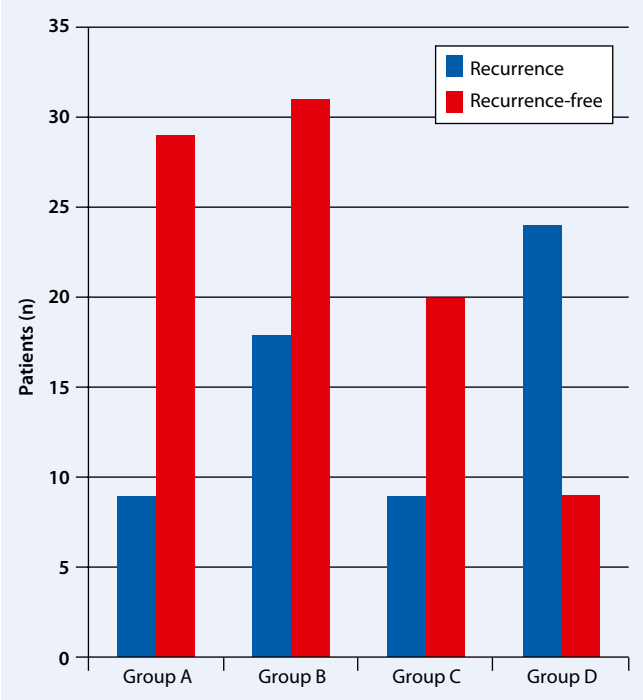

Fig. 3 ▲ Recurrent atrial tachyarrhythmias in four groups (*A*, *B*, *C*, and *D*) based on combined HbA1c and left atrial size

of HbA1c in the development of atrial fibrosis and atrial structural remodeling should be investigated further.

Corresponding address

C.-S. Ma
Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University
2 Anzhen Road, 100029 Beijing
Chaoyang District
P.R. China
chshma@vip.sina.com

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Compliance with ethical guidelines

Conflict of interest. Z.-H. Lu, N. Liu, B. Rai, Y. Yao, S.-N. Li, R.-H. Yu, C.-H. Sang, R.-B. Tang, D.-Y. Long, X. Du, J.-Z. Dong, and C.-S. Ma state that there are no conflicts of interest. All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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