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Association of Obesity Measures with Atrial Fibrillation Recurrence After Cryoablation in Patients with Paroxysmal Atrial Fibrillation

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Background: Obesity increases the risk of atrial fibrillation (AF) recurrence after ablation. This study explored the relationship between various obesity indexes and risk of recurrence after cryoablation of paroxysmal AF (PAF).

Material/Methods: Our prospective study included 100 patients with PAF who underwent first cryoablation. Physical examination and fasting blood lipids levels were measured at baseline. Seven obesity indexes were determined: body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), waist-hip ratio (WHR), cardiometabolic index (CMI), lipid accumulation product (LAP), and body adiposity index (BAI). AF recurrence was confirmed by electrocardiograms and Holter monitor at follow-up visits after the initial 3-month blanking period. Receiver operating characteristic (ROC) curves were drawn to assess the abilities of obesity indicators in predicting AF recurrence. Multivariable Cox regression analysis was used to examine independent predictors of AF recurrence.

Results: During a mean follow-up of 13.4 months, 31 patients (31.0%) had recurrent AF. Patients with recurrence had higher BMI, WC, WHtR, LAP, and BAI compared with those without recurrence. ROC analysis indicated the potential predictive value of BAI with an AUC of 0.657 (95% confidence interval [CI]: 0.534–0.779), followed by WC, WHtR, LAP, and BMI (all $P<0.05$). Diagnosis-to-ablation time (HR 1.034, 95% CI: 1.002–1.068), left atrial diameter (HR 1.147, 95% CI: 1.026–1.281), and WC (HR 1.026, 95% CI: 1.000–1.053) were independent predictive factors for AF recurrence after multivariable adjustment.

Conclusions: In this study population, WC appears to be a potential indicator for the prediction of recurrence in patients with PAF after cryoablation.

MeSH Keywords: **Atrial Fibrillation • Body Mass Index • Obesity • Recurrence • Waist Circumference**

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Background

Catheter ablation is the recommend strategy for symptomatic paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (persAF) in current guidelines and expert consensus worldwide [1,2]. Radiofrequency ablation and cryoablation are the 2 most commonly used ablation energy sources. Recently, more and more randomized controlled trials, cohort studies, and meta-analyses have shown that the efficiency and safety of cryoablation is not inferior to radiofrequency ablation [3–6]. Second-generation cryoballoon (2G-CB) ablation has been widely used in hospitals worldwide. However, the overall success rate of cryoablation for AF is not ideal. Previous meta-analysis studies have shown that the 1-year success rate of PAF is about 80%, while it is only about 70% in patients with persAF [7,8]. It is, thus, crucial to identify the particular characteristics of patients with recurrence after cryoablation.

Overweight or obesity is related to poor outcomes in patients with AF following ablation [9]. Previous studies have explored the association between body mass index (BMI), the most widely used clinical indicator for evaluating obesity, and AF recurrence after ablation. A recent published article reports the result from the ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry, which shows that a baseline BMI ≥30 kg/m^2 can increase the recurrence rate of AF after ablation [10]. An earlier meta-analysis including 6 observational studies shows that patients with overweight and obesity had 27% and 38% increased risk of AF recurrence, respectively [11]. However, BMI does not consider the distribution of body fat and cannot distinguish lean tissue from fat [12]. Therefore, other indicators of obesity, such as waist circumference (WC), waist-to-height ratio (WHtR), waist-hip ratio (WHR), and other novel indicators, such as lipid accumulation product (LAP), cardiometabolic index (CMI) and body adiposity index (BAI), have been developed. Nevertheless, to the best of our knowledge, there has been no study evaluating the correlation intensity of various obesity indicators in predicting AF recurrence after ablation.

Thus, we designed a single-center study to determine the association of obesity indicators, including traditional indexes and novel indicators, with the risk of arrhythmia recurrence after cryoablation in PAF patients.

Material and Methods

Ethics approval

This study plan was approved by the Medical Ethics Committee of our hospital, and conformed to the principles of the Declaration of Helsinki. All participants provided written informed consent for participation on admission.

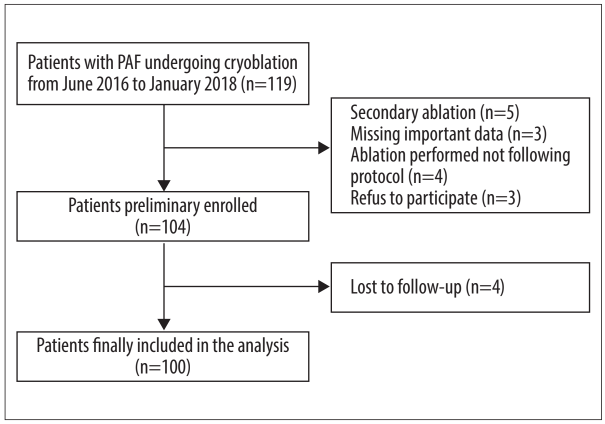

Figure 1. Flow diagram describing the study population.

Study participants

From June 2016 to January 2018, 100 consecutive patients with PAF who underwent first 2G-CB ablation procedure in Xinjiang Medical University, Affiliated Hospital One were recruited (Figure 1). PAF was defined as AF episodes cardioverted within 7 days after onset, as stated by the 2016 European Society of Cardiology AF guidelines [1]. We excluded patients with persAF, long-standing persAF, abnormal pulmonary vein anatomy, left atrial (LA) thrombosis, hyperthyroidism, refractory heart failure (left ventricular ejection fraction <40%), severe valvular heart disease, LA diameter >55 mm, previous ablation, anticoagulant contraindications, or for whom important data were missing.

Baseline data collection and definitions

Baseline information on demographic characteristics, medical history, electrocardiogram (ECG) and echocardiography were obtained from the electronic medical record system. We measured P-wave duration (PWD) of lead II in sinus rhythm ECG before ablation using a GetData Graph Digitizer (version 2.26). This data was taken as the average of 5 consecutive PWDs. Diagnosis-to-ablation time (DTAT) was defined as the time between the first report of AF diagnosis and the day of the ablation procedure [13].

Physical examination data, including height, weight, WC, and hip circumference, was obtained by standard methods at the time of admission with patients wearing light clothing. WC was measured at 1 cm above the umbilical level at minimal breathing. Hip circumference was measured at the level of maximum extension of the hip. BMI, WHR, and WHtR were calculated as follows: weight divided by height squared (kg/m^2), WC divided by hip circumference (cm/cm), and WC divided by height (cm/cm), while BAI was calculated using the formula: (Hip circumference/Height$^{1.5}$–18).

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Blood samples were collected at the second day after admission after 12 h of overnight fasting. The level of blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides), alanine aminotransferase (ALT), creatinine (Cr), and fasting blood glucose (FBG) were measured using an automatic biochemical analyzer (AU640, Beckman Coulter, Inc., USA). LAP was calculated using the following sex-specific formula: [WC (cm)–65]×[triglyceride (mmol/L)] in males and [WC (cm)–58]×[triglyceride (mmol/L)] in females. CMI was calculated as WHtR×(triglyceride/HDL-cholesterol).

2G-CB ablation procedure

Patients received regular anticoagulant therapy during the first 3 weeks before ablation. All antiarrhythmic medications were stopped at least 5 half-lives before ablation.

All patients underwent pulmonary vein (PV) isolation (PVI) using 2G-CB ablation. Electrophysiological examination and ablation procedure were performed in an awake state. Fentanyl and midazolam were used for analgesia. PV angiography was performed after atrial septal puncture, and then the cryoballoon sheath was placed. A 2G-CB (Arctic Front Advance™, Medtronic, Inc., USA) with a mapping catheter (Achieve™, Medtronic, Inc., USA) was delivered to the LA via the cryoballoon sheath. The mapping catheter was sent into the target PV to map and record PV potentials. The 2G-CB was introduced into the target PV to block the mouth of PV after being fully expanded. Two freezing cycles lasting 180 s were performed for each PV. No additional ablation or other non-PV triggers were performed. If the balloon temperature was below -55°C, freezing was terminated immediately. PVI was confirmed by the Achieve catheter after each freezing cycle. When the right PV was being cryoablated, a 4-pole electrode was introduced into the superior vena cava for continuous pacing of the phrenic nerve. Diaphragmatic muscle movement was observed under fluoroscopy. If diaphragmatic movement was weakened or disappeared, the 2G-CB ablation was immediately terminated.

Postoperative management and follow-up

After ablation, all patients took anticoagulants and proton-pump inhibitors for 4 weeks. Based on each individual's CHA_2DS_2-VASc score, it was decided whether to continue anticoagulant treatment or not. Antiarrhythmic drugs were used based on individual clinical decision, and continued for the maximum of 3 month after ablation.

ECG and Holter monitoring were conducted at 3, 6, and 12 months after intervention. Patients were asked to contact our study team if they had any discomfort. The initial 3 months after ablation were defined as the blanking period. The endpoint definition for this study, AF recurrence, was any symptomatic or asymptomatic atrial tachyarrhythmia (atrial tachycardia, atrial flutter, and/or AF) lasting >30 s documented in ECG or Holter monitor after the blanking period.

Table 1. Study population characteristics.

Characteristic	n=100
Age, years	59.99±9.90
Male, n (%)	59 (59.0)
Hypertension, n (%)	56 (56.0)
Diabetes, n (%)	19 (19.0)
Coronary artery disease, n (%)	30 (30.0)
Pacemaker, n (%)	8 (8.0)
Left atrial diameter, mm	38.44±5.41
Left ventricular ejection fraction, %	62.10±4.87

Statistical analysis

Data analysis was performed using SPSS software (version 23.0). Continuous data are presented as means±standard deviation or median (quartiles), and were assessed by the *t* test or Mann-Whitney U test. Classified data are presented as proportions and were evaluated by chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to assess the intensity of obesity indicators in predicting AF recurrence after ablation. Variables with *P* value <0.05 in analysis comparing patients with and without AF recurrence were included in multivariable Cox regression analysis to assess the independent factors in predicting AF recurrence. Kaplan-Meier analysis was used to compare the probability of AF recurrence based on the cut-off point determined from the ROC curve. A *P* value <0.05 was considered statistically significant.

Results

Study population characteristics and outcome

This study enrolled 100 patients; baseline clinical characteristics are delineated in Table 1. Briefly, 59.0% of patients were male and the mean age was 59.99±9.90 years. The most frequent concomitant disease was hypertension, which was diagnosed in 56.0% of patients. AF recurrence was detected in 31 patients (31.0%) during a mean follow-up of 13.4±4.1 months.

Comparison of baseline characteristics

Patients were divided into 2 groups according to whether they had AF recurrence. The comparison of baseline clinical data of the 2 groups is shown in Table 2. There were no significant

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Table 2. Clinical baseline data compared between patients with and without recurrence of AF.

Variables	No AF recurrence (n=69)	AF recurrence (n=31)	*P* value
Age, years	60.25±10.18	59.42±9.40	0.701
Male, n (%)	38 (55.1)	21 (67.7)	0.234
Diagnosis-to-ablation time, months	11 (6, 18)	18 (12, 26)	<0.001
Hypertension, n (%)	38 (55.1)	18 (58.1)	0.780
Diabetes, n (%)	14 (20.3)	5 (16.1)	0.624
Coronary artery disease, n (%)	19 (27.5)	11 (35.5)	0.422
Transient ischemic attack/stroke, n (%)	17 (24.6)	6 (19.4)	0.562
Pacemaker, n (%)	5 (7.2)	3 (9.7)	0.679
P-wave duration, ms	109.63±10.64	111.84±13.29	0.377
Left atrial diameter, mm	37.17±5.29	41.26±4.60	<0.001
Right atrial diameter, mm	35.75±4.20	36.55±4.36	0.389
Left ventricular ejection fraction,%	62.46±4.51	61.29±5.59	0.268
CHA_2DS_2-VASc score	2 (1, 3)	2 (1, 4)	0.912
Antiarrhythmic drugs	40 (58.0)	22 (71.0)	0.216
Body mass index, kg/m^2	25.90±3.71	28.47±5.41	0.007
Waist circumference, cm	86.38±13.50	95.29±16.00	0.005
Waist-to-hip ratio	0.93±0.05	0.93±0.04	0.924
Waist-to-height ratio	0.52±0.07	0.57±0.09	0.007
Cardiometabolic index	0.62 (0.36, 1.14)	0.70 (0.54, 0.95)	0.342
Lipid accumulation product	29.16 (17.36, 44.51)	39.20 (24.85, 57.34)	0.031
Body adiposity index	25.22 (21.97, 28.29)	30.32 (23.79, 34.13)	0.013
Total cholesterol, mmol/L	3.87±0.91	3.81±0.94	0.756
Triglyceride, mmol/L	1.65±1.12	1.48±0.59	0.448
LDL-cholesterol, mmol/L	2.41±0.81	2.44±0.79	0.845
HDL-cholesterol, mmol/L	1.19±0.37	1.13±0.28	0.441
ALT, mmol/L	20.50±11.81	24.10±11.20	0.155
Creatinine, umol/L	70.88±19.82	70.78±16.52	0.981
Fasting blood glucose, mmol/L	5.44±1.48	5.72±1.45	0.393

differences between the 2 groups in age, sex, hypertension, diabetes, coronary artery disease, transient ischemic attack/stroke, pacemaker, PWD, right atrial diameter, left ventricular ejection fraction, CHA_2DS_2-VASc score, antiarrhythmic drugs, WHR, CMI, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, ALT, Cr, or FBG (P value >0.05). A higher DTAT, LA diameter, BMI, WC, WHtR, LAP, and BAI were observed in the patients with AF recurrence compared with patients without recurrence.

Accuracy of obesity indicators in predicting AF recurrence

According to the results of ROC analysis (Table 3, Figure 2), the largest area under the curve (AUC) was observed for BAI (AUC 0.657, 95% CI: 0.534–0.779), WC with an AUC of 0.650 (95% CI: 0.526–0.774), WHtR with an AUC of 0.643 (95% CI: 0.519–0.766), LAP with an AUC of 0.635 (95% CI: 0.523–0.748), and BMI with an AUC of 0.634 (95% CI: 0.506–0.763). However, no significant differences in the AUCs for WHR and CMI were found in the ROC analysis.

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Table 3. ROC analysis of obesity indicators.

Variable	AUC	95% CI	*P* value
Body mass index	0.634	0.506–0.763	0.032
Waist circumference	0.650	0.526–0.774	0.017
Waist-to-hip ratio	0.504	0.379–0.628	0.955
Waist-to-height ratio	0.643	0.519–0.766	0.023
Cardiometabolic index	0.560	0.449–0.670	0.342
Lipid accumulation product	0.635	0.523–0.748	0.031
Body adiposity index	0.657	0.534–0.779	0.013

ROC – receiver operating characteristic curves; AUC – area under the ROC curves; CI – confidence interval.

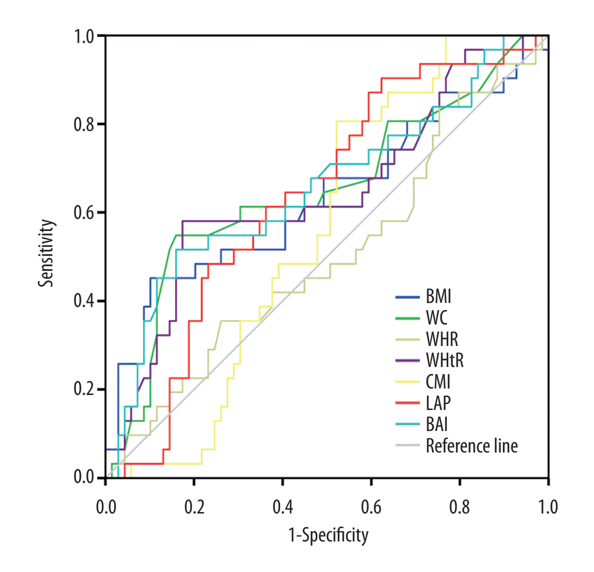

Figure 2. Receiver operating characteristic curves of the predictive value of obesity indicators for AF recurrence.

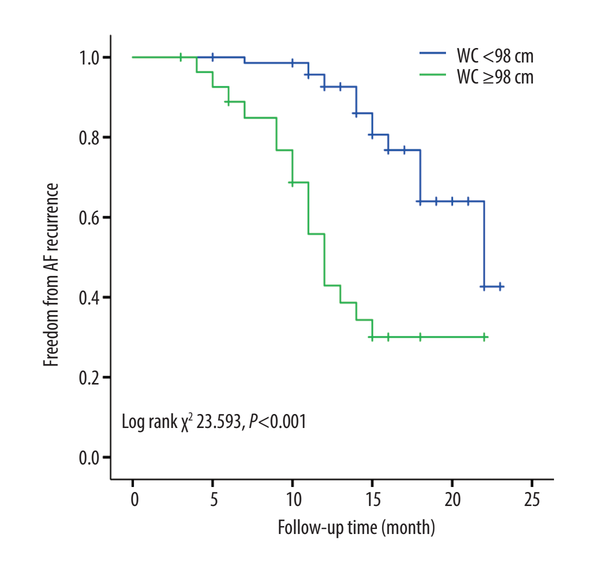

Figure 3. Kaplan-Meier plots of AF recurrence rate for 2 WC groups.

Table 4. Risk factors for atrial fibrillation recurrence.

Variable	β	SE	Wald χ^2	HR (95%CI)	*P* value
DTAT (per month increment)	0.034	0.016	4.322	1.034 (1.002–1.068)	0.038
LA diameter (per mm increment)	0.137	0.057	5.816	1.147 (1.026–1.281)	0.016
WC (per cm increment)	0.026	0.013	3.844	1.026 (1.000–1.053)	0.050

HR – hazard ratio; CI – confidence interval; DTAT – diagnosis-to-ablation time; LA – left atrium; WC – waist circumference.

Risk factors of AF recurrence

Because WC and TG levels are components of LAP, a forward stepwise selection procedure was conducted in a multivariable Cox proportional hazards model. Cox regression analysis demonstrated that DTAT [hazard ratio (HR) 1.034, 95% confidence interval (CI): 1.002–1.068] and LA diameter (HR 1.147, 95% CI: 1.026–1.281) were independent predictive factors for AF recurrence (Table 4). After adjusting for other factors, WC is the only obesity index that was borderline associated with AF recurrence (HR 1.026, 95% CI: 1.000–1.053). Kaplan-Meier curves suggest a higher AF recurrence rate after cryoablation in PAF patients with higher WC (log rank χ^2=23.593, P<0.001, Figure 3).

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Discussion

Main findings

We explored the correlation between different obesity indexes and recurrence of AF after 2G-CB ablation, and compared the association intensity. We found that BMI, WC, WHtR, LAP, and BAI were associated with AF recurrence. After forward stepwise selection, WC was the only independent predictive obesity indicator associated with AF recurrence.

Obesity and AF recurrence

AF and obesity have become worldwide public health problems, and identifying the correlation between these 2 conditions is important for early intervention. Obesity is a known independent risk factor for new-onset AF, but results of the association between obesity and AF recurrence after ablation are inconsistent [14,15]. In a previous study, AF recurrence was not found to be associated with BMI in patients with symptomatic PAF and persAF after wide circumferential electrical PVI [16]. Results from the Guangzhou AF ablation registry show that BMI has a "U"-shaped effect on ablation outcome, and the risk of AF recurrence in obesity patients with BMI ≥30 kg/m^2 was 78% higher (95% CI: 1.17–2.72) than in normal-BMI patients [9]. Similarly, results from the ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry, the largest multicenter cohort study to date examining the association between BMI and AF recurrence after radiofrequency ablation, indicate that obesity increases the recurrence rate of AF compared with overweight patients [10]. A meta-analysis which included 12 studies and 3286 AF patients showed that high BMI led to a 1.32-fold (95% CI: 1.17–1.5) increased likelihood of AF recurrence compared with normal-BMI patients [17]. However, the pooled estimate of odds ratio did not reach significance after adjusting for multiple confounders [17]. Our findings are the same as most of the above studies, supporting BMI as a risk factor for recurrence after AF ablation. Obesity is associated with conditions verified to be related to AF recurrence, such as obstructive sleep apnea, and these concomitant diseases might partly explain the relationship between obesity and AF recurrence and these conflicting results [18].

Different obesity indicators in predicting AF recurrence

BMI and WC are the 2 commonly used measures for evaluating general (peripheral) obesity and central (abdominal) obesity, respectively. Recently, new adiposity phenotypes, like BAI, CMI, and LAP, have been developed for evaluating obesity, which combine anthropometric factors and simple biochemical factors. Some studies have shown that these new adiposity indices are more accurate in predicting chronic diseases like hypertension and ischemic stroke [19,20]. However, our results show that these new obesity indices are not superior in predicting AF recurrence compared with WC. This may be because the new indicators contain blood lipid indexes. Although hyperlipidemia is a well-established risk factor for cardio-cerebrovascular diseases, a "cholesterol paradox" phenomenon has been found in AF [21]. A recent prospective study indicates that fasting levels of total cholesterol and LDL-cholesterol were negatively correlated with recurrence after ablation in women, and lipid indexes were not independently correlated with AF recurrence in men [22]. This might explain why WHtR reaches statistical significance, while CMI, which combines WHtR and lipid indexes, did not reach statistical significance in our univariate analysis. Compared with BMI, WC reflects the content of visceral fat, indicating the body's metabolic disorder and inflammatory response, which may improve its ability to predict AF recurrence after ablation [23].

Although obesity indicators can predict the recurrence of AF after ablation, the ROC analysis in our study showed that obesity indicators only have a slight predictive value, which is similar with a previous study [9]. This may be due to the complexity of the pathophysiological basis and triggering mechanism of AF recurrence after ablation. A single clinical indicator might have poor sensitivity and specificity in predicting AF recurrence.

Other predictors of AF recurrence

Different studies reported inconsistent risk factors or predictors of AF recurrence, and this might be influenced by differences in baseline patient characteristics, ablation strategies, recurrence definitions, follow-up time, and variables included in the multivariate analysis. Consistent with most previous studies, our study showed that enlarged LA diameter increases the risk of AF recurrence, which has been widely confirmed in large observational studies and meta-analyses [24,25].

AF progression is an important cause of poor clinical outcome for AF patients [26]. Previous studies have shown that obesity can induce the initiation of AF and also has a pivotal role in promoting AF progression by increasing the release of inflammatory factors, promoting atrial fibrosis, and increasing epicardial adipose tissue and pericardial fat [27,28]. The widely accepted "AF begets AF" theory states that AF itself can promote the development of AF by progressive electrical and structural remodeling, finally making AF irreversible [29,30]. Therefore, the longer the AF duration lasts, the more severe the atrial substrate remodeling, and the worse the therapeutic effect of catheter ablation tends to be. However, it is difficult to accurately quantify the true duration of AF in clinical practice, and DTAT is a relatively reliable and simple indicator of the duration of AF before ablation. In our study, univariate and multivariate analysis showed that DTAT has significant predictive value. Similar conclusions have been reported in both a single-center study [31] and a multicenter study [13], as well as

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in cohorts composed of patients with PAF only [32] and cohorts composed of patients with persAF only [33]. A recent meta-analysis of 6 studies also showed that the HR for AF recurrence of DTAT was 1.19 (95% CI: 1.02–1.39) [34]. Obesity and longer DTAT are both factors for AF progression, and in our study they were confirmed to be risk factors for recurrence after cryoablation. Therefore, we advocate that for obese patients with AF who meet the indications for catheter ablation, ablation should be performed as early as possible to improve the ablation success rate. In addition, a previous study demonstrated that shorter DTAT is associated with lower cardiovascular hospitalization [35], so early interventions can have additional clinical benefits. Obesity can increase the burden and severity of AF symptoms on patients, so obese patients with AF may seek medical treatment earlier than those with normal weight [36]. This suggests that physicians should pay more attention to DTAT in obese patients with AF.

ECG is a simple, noninvasive, and low-cost detection method of arrhythmia and cardiac electrical activity. A recent meta-analysis showed that prolonged PWD was associated with AF recurrence, despite normal LA size [37]. However, our study failed to find differences in PWD in lead II of sinus rhythm ECG before ablation between patients with and without AF recurrence, perhaps because we calculated the PWD manually, which might have made our results less accurate. In addition, the DTAT of our study population was relatively shorter and LA diameter was smaller compared with other studies. The degree of left atrial structural remodeling is expected to be less, so the difference in PWD between the 2 groups might be much smaller. Identification of predictors of AF recurrence following ablation is very important, but we believe that the simplicity, universality, consistency, and clinical practicality of these indicators are even more important. Previous studies have suggested that several P-wave morphological indices, such as PWD, P-wave dispersion, and P-wave terminal force, are associated with AF recurrence [38,39]. Therefore, more stable and reliable markers in the ECG are needed to help identify patients with higher risk of AF recurrence.

Predictive models with multiple predictive factors may be more clinically applicable and deliver more information than a single indicator. Several studies have already established predictive scores for AF recurrence after ablation, but these scores are contradictory to each other [40–42]. For example, in the CAAP-AF score [41] and ATLAS score [42], female sex is a risk factor for AF recurrence, but in the MB-LATER score [43], male sex is a risk factor for AF recurrence. This may be due to their small sample sizes and the differences in baseline data of these studies. Further research is needed to provide more accurate and personalized recurrence risk predictions in future large-sample cohort studies by combining big data of clinical characteristics, AF characteristics, electrophysiological indicators, and serological indicators.

Importance of lifestyle management in obese AF patient

Despite great advances in ablation techniques, the success rate of AF ablation is still not ideal. Patient selection is the first and perhaps the most important step in improving ablation prognosis. There are clinical benefits to optimizing the management of modifiable risk factors. Our results show that obesity aggravates late recurrence after AF cryoablation, emphasizing the importance of lifestyle management in obese AF patients. A cohort study with up to 5 years of follow-up showed that long-term sustained weight loss can significantly reduce AF burden and maintain sinus rhythm [44]. Obesity is associated with a variety of comorbidities, such as hypertension, diabetes, and sleep apnea, which are all associated with progression of the atrial substrate and the development of AF [45]. Appropriate lifestyle management and weight loss systematically reduce these related risk factors and proarrhythmic mechanisms, and both might be highly effective in reducing AF recurrence in obese patients after ablation [46].

Limitation

There were several limitations to our study. First, this was a single-center study with a short follow-up period, and the simple size was relatively small. Additionally, the inclusion of learning curve cases may have caused inaccuracies in assessment of recurrence risk factors. Second, the follow-up visits only included ECG and Holter monitoring, and thus might have underestimated the recurrence rate of AF. Third, some baseline information related to AF recurrence was not included, which might have biased the results of multivariable Cox regression analysis. Fourth, we did not consider weight changes during follow-up, but weight management might improve the long-term success of AF ablation. Further prospective studies with longer follow-up period in other populations and large-sample cohorts are necessary to verify our results.

Conclusions

WC could be considered an appropriate potential obesity indicator for the prediction of AF recurrence after cryoablation. Lifestyle management might be recommended in obese AF patients before undergoing cryoablation.

Acknowledgments

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Conflict of interest

None.

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