European Review for Medical and Pharmacological Sciences 2020; 24: 4997-5007

Functional studies of left atrium and BNP in patients with paroxysmal atrial fibrillation and the prediction of recurrence after CPVA

M. XU[1,2], F. LIU[2], Z.-X. GE[2], J.-M. LI[3], X. XIE[4], J.-H. YANG[1]

[1]Department of Echocardiography, The First Affiliated Hospital of Soochow University of Jiangsu Province, SuZhou, China
[2]Department of Echocardiography, [3]Department of General Surgery, [4]Department of Ultrasound; The Third Affiliated Hospital of Soochow University of Jiangsu Province, ChangZhou, China

Abstract. – OBJECTIVE: This study was aimed to observe the significance of the left atrium (LA) functional index combined with B-type natriuretic peptide (BNP) level in predicting recurrence in patients with paroxysmal atrial fibrillation (PAF) after circumferential pulmonary vein ablation (CPVA). Real-time three-dimensional echocardiography (RT-3DE) was used to observe the structural and functional changes of LA in patients with PAF after CPVA. BNP is a hemodynamic indicator of myocardial stretching increase in atrial fibrillation (AF) patients.

PATIENTS AND METHODS: 243 patients with PAF who intended to undergo CPVA were selected in the study, and the following clinical data of the patients were collected. Firstly, the blood BNP levels measured before CPVA. Secondly, the measurements of routine echocardiography before CPVA. RT-3DE was used to obtain the time-volume curve of LA. Then, multivariate logistic regression analysis was used to analyze the factors affecting PAF recurrence after CPVA. Finally, we obtained the receiver operating characteristic (ROC) curve of PAF recurrence predicted by the independent risk factors.

RESULTS: A total of 233 AF patients with an average age of 63.1 ± 9.3 years (range, 39-75 years; male: female =195: 38) underwent CPVA. 42 patients had AF recurrence (18.0%) during 3-6months follow-up after an operation blanking period of 3 months, BNP in the Recurrence Group was higher than that in Sinus Rhythm Group ($p \leq 0.001$). The preoperative left minimum volume index (LAVImin), left atrial volume index before contraction (LAVIpre-a) were higher in Recurrence Group than in Sinus Rhythm Group ($p \leq 0.001$). Expansion index, Diastolic emptying index (DEI), Passive emptying index (PEI), Active emptying index (AEI) were lower in the Recurrence Group than in the Sinus Rhythm Group ($p \leq 0.001$). Logistic regression analyses showed that BNP and DEI were independent predictors for PAF recurrence (OR=1.004, 95% CI: 1.01-1.07, p=0.001; OR=0.655, 95% CI: 0.57-0.75, p=0.001). The AUC of BNP, DEI and combined index for recurrence of CPVA were higher than LAVImax (p range: 0.001-0.013).

CONCLUSIONS: In patients with PAF treated with CPVA, the impaired DEI of LA reservoir function and increased BNP may be useful predictors of PAF recurrence.

Key Words:
Atrial fibrillation, B-type natriuretic peptide, Circumferential pulmonary vein ablation, Recurrence.

List of Abbreviations

LA = left atrium; AF = atrial fibrillation; PAF = paroxysmal atrial fibrillation; BNP = B-type natriuretic peptide; CPVA = circumferential pulmonary vein ablation; AAD = antiarrhythmic drug; CMRI = cardiac magnetic resonance imaging; CT = computed tomography; TEE = transesophageal echocardiography; SEC = spontaneous echocardiographic contrast; RT-3DE = real time- three dimensional echocardiography; LAVI = left atrium volume index; LAVImax = left atrial maximum volume index; LAVImin = left atrial minimum volume index; LAVIpre-a = left atrial volume index before contraction; PE = passive emptying percentage of total emptying; AE = active emptying percentage of total emptying; DEI = diastolic emptying index; PEI = passive emptying index; AEI = active emptying index; LAA = left atrial appendage; LAAV = left atrial appendage peak emptying velocity; LVEF = left ventricular ejection fraction; NOACs = non-vitamin K antagonist oral anticoagulants; ROC = receiver operating characteristic; ECG = electrocardiograph.

Corresponding Authors: Junhua Yang, MD; e-mail: yangjhsz1@163.com
Jumei Li, MD; e-mail: yuetao-w1@163.com
Xiao Xie, MD; e-mail: loisice@sohu.com

Introduction

Atrial fibrillation (AF) is one of the most common and dangerous arrhythmias. Remodelling of atrial structure and ion channel function are important mechanisms leading to atrial fibrillation[1]. As first-line treatment for paroxysmal atrial fibrillation (PAF), the multicenter clinical randomized trial strongly support the use of catheter ablationin patients with who do not respond to initial antiarrhythmic drug (AAD)[1]. Although in the CABANA trial of symptomatic patients with AF, there was no significant difference between catheter ablation group and drug therapy group in the primary endpoint and the all-cause death group, catheter ablation (including circumferential pulmonary vein ablation, CPVA) led to a substantial reduction of recurrence of atrial fibrillation at 12 months[2]. The CPVA is superior to the single AAD for PAF patients in the recurrent atrial tachyarrhythmias of 9 and 24 months follow-up[3], stroke, cardiovascular events[4] and mean quality of life scores. Furthermore, ablated patients receiving AAD are less likely to atrial tachyarrhythmias compared to ablated patients kept free from AAD[5,6]. However, the recurrence rate after CPVA can reach 20%-40%[2], and about 50% of patients relapse in 24 months after a single operation. As the high recurrence rate is still a widespread concern, and the mechanism and related factors of recurrence remain unclear, it is imperative to find indicators that can predict the CPVA recurrence.

LA dilation precedes or appears early after the onset of AF and is involved in the progression of arrhythmia. Left atrium maximum volume (LAVmax) is a risk factor of the recurrence after CPVA and thromboembolic risk in patients with AF[7]. Later in-depth studies of LA function have demonstrated that LA remodeling is closely related to the recurrence after CPVA. AF is a progressive disease that can alter the original electrical and structural features during the remodeling process. Atrial remodeling is a major characteristic of AF, which provides a heterogeneous environment for electrical propagation, and triggers recurrence activity[8]. RT-3DE is a new method for evaluating LA remodeling, which is more sensitive to LA dysfunction. The measurement of atrioventricular scale by the RT-3DE is highly correlated to the gold standard of cardiac magnetic resonance imaging (CMRI) and computed tomography (CT)[9].

Brain natriuretic peptide (BNP) is a biologically active circulating hormone secreted by the heart and belongs to the natriuretic peptide family (NPs). The secretion of BNP includes the regulatory secretion of atrial and the structural secretion of the ventricle. Left atrial volume and pressure load in AF patients are essential factors regulating BNP secretion[10]. The BNP in AF patients is mainly involved in the diuresis, sodium excretion, vasodilation and inhibition of aldosterone synthesis[11]. BNP is elevated in AF patients without heart failure, and meta-analysis has shown that the elevated baseline BNP levels were associated with an increased risk of AF recurrence after catheter ablation, suggesting that BNP may be a biomarker for predicting AF recurrence[12].

In AF patients with LA remodeling, volume increase, and elevated atrial tension, the heart produces precursor Pro-BNP in pulse, which is converted to biologically active BNP. BNP is released from the myocardium when it is exposed to stretch and increased wall stress. The most important stimulus for cardiac secretion of BNP is the myocardial cell stretch, and the increase in the plasma BNP concentration is related to the amount of stretch[13]. Therefore, the plasma BNP concentration reflects the degree of myocardial stretching and stress changes in the ventricular wall[14].

We used RT-3DE to dynamically assess the volume and function of LA before and after CPVA in patients with PAF. The structural remodeling of LA was evaluated by the advanced three-dimensional ultrasound imaging technology, and combined with the critical biomarker BNP, the power of LA ultrasound index in predicting PAF recurrence was quantified. Through these examinations, we aimed to optimize the invasive rhythm control strategy of AF patients.

Patients and Methods

Patients

Between January 2017 and August 2019, 243 patients with paroxysmal symptomatic AF who were hospitalized for the first time for CPVA were enrolled. PAF was defined as that AF terminated spontaneously within 7 days, mostly < 24 hours. All patients had taken more than one antiarrhythmic drug, including 38 women and 205 men. All patients met the following criteria: (1) no history of organic heart diseases, such as coronary heart disease, hypertensive heart disease, cardiomyopathy, valvular disease, or congenital

heart disease; (2) no clinical cardiac dysfunction symptoms and signs, and no preoperative echocardiographic evidence of cardiac dysfunction [left ventricular ejection fraction (LVEF) ≥ 50%], no liver or kidney dysfunction; (3) no respiratory disease; (4) clinical symptoms observed at the onset of AF. At baseline, all patients were examined by the physician and obtained the following information: history, current symptoms, functional grading, medication, height, weight, non-invasive blood pressure, renal function, heart rate, 12-lead electrocardiograph (ECG). All patients provided written informed consent according to the Declaration of Helsinki and the study was approved by the Scientific Ethics Committee.

Blood Sample Collection and Measurements

Blood was collected in the morning before CPVA when the patient was in sinus rhythm. According to the recommendations of the European Society of Cardiology practical guidance[15] and CardioOrmocheck study[16], 2 ml of blood was obtained from each patient in Ethylene Diamine Tetraacetic Acid (EDTA) anticoagulation test tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), when fasting, and under supine position. The supernatant was taken after centrifugation at 3000 r/min for 10 min in 2 hours and processed with AU5800 automatic immunoassay instrument (Beckman Coulter, Brea, CA, USA) using chemiluminescence method, according to the Biosite BNP assay[17], lower detection limits of 10 pg/ml.

Echocardiography

Conventional echocardiography, transesophageal echocardiography (TEE) and RT-3DE (Epic 7C, Philips Healthcare Royal Philips Electronics, Amsterdam, The Netherlands) were performed before CPVA according to the recommendations of the European Association of Cardiovascular Imaging (EACVI)[18]. The 243 PAF patients laid down in the left lateral position and connected with a 12-lead ECG, and the images were acquired at parasternal and apical views using an X5-1 and X7-2 probe with 15 cm in depth. The average frame rate was 50 frames/second. Standard Motion(M-), two-dimensional (2D) and three-dimensional (3D) images were obtained. All echocardiographic images were digitally stored, and the measurements of volume and functions were conducted by the commercially available QLAB (10.5; Philips Healthcare Royal Philips Electronics, Amsterdam, The Netherlands) software package. Five cardiac cycles in full-volume were continuously obtained from AP4 (apical four-chamber heart) for 3D analysis which requires an optimal breath-hold[19] within three days before CPVA. We acquired images during sinus rhythm in PAF patients. The interval between blood test and echocardiography was no more than one hour. The images were analyzed by two experienced doctors on the same day. The ejection fraction was calculated using the biplane Simpson's method. All TEEs were performed using an X7-2 probe by a senior certified echocardiography cardiologist, in order to observe the LA and left atrial appendage (LAA) for thrombosis and spontaneous echocardiographic contrast (SEC), and at the same time, left atrial appendage peak emptying velocity (LAAV) were obtained from the TEE. The LA volume-time curve of the whole cardiac cycle was obtained by RT-3DE, which yielded the measurements for maximum LA volume (LAVmax), minimum LA volume (LAVmin), and the LA volume before atrial active contraction (LAVpre-a). LAVpre-a was measured at the beginning of P wave in surface electrocardiogram. All LAVs were normalized by body surface area. The left atrial function was derived from the following formulas.

Reservoir function was assessed using the following two indices:

(1) Expansion index = [(LAVImax-LAVImin)/LAVImin] × 100%

(2) Diastolic emptying index (DEI) = [(LAVImax-LAVImin)/LAVImax] × 100%.

Conduit function was assessed using the following two indices:

(1) Passive emptying percentage of total emptying (PE) = [(LAVImax-LAVIpre-a)/ (LAVImax-LAVImin)] × 100%

(2) Passive emptying index (PEI) = (LAVImax-LAVIpre-a)/ LAVImax × 100%.

Booster pump function was assessed using the following two indices:

(1) Active emptying percentage of total emptying (AE) = [(LAVIpre-a-LAVImin)/ (LAVImax-LAVImin)] × 100%

(2) Active emptying index (AEI) = (LAVIpre-a-LAVImin)/ LAVIpre-a × 100%.

Percutaneous Radiofrequency Ablation

Catheter ablation was performed using a 3-dimensional electroanatomic mapping system (CARTO, Biosense Webster, Diamond Bar, CA, USA) to

support the creation and validation of radiofrequency lesions. All patients discontinued at least 5 half-life other antiarrhythmic drugs except amiodarone. Both an ablation catheter and a circular catheter for registry and stimulation (Lasso, Biosense Webster; or Inquiry Optima, St. Jude Medical, MN, USA) were introduced percutaneously through the femoral vein. A double transseptal puncture was performed to access the LA. Three radio frequencies were delivered through an irrigated-tip thermocouple-equipped catheter (3.5 mm) using a target temperature of 45°C at 40 W. Radiofrequency lesions were made surrounding each ipsilateral pulmonary vein as previously described. The target was the reduction of local electrogram to < 0.15 Mv and elimination of pulmonary vein potentials with the establishment of bidirectional conduction block between the LA and pulmonary veins.

Postoperative Treatment, Follow-Up, and Grouping

The electrocardiogram was performed every day for 3 days after CPVA, and non-vitamin K antagonist oral anticoagulants (NOAC) was given for 2 months after surgery. All patients continued to use a previously antiarrhythmic drug treatment for 3 months after surgery (amiodarone, 200 mg, Qd; propafenone 150 mg, Tid or morerazine 150 mg, Tid; sotalol 80 mg, Bid). All patients were followed up for a minimum of 3 months and up to 6 months (healing period). The follow-up phone number and the fax of ECG data were collected. The Holter examination was followed up monthly after discharge. AF recurrence occurring in the first 3 months after the ablation (blanking period) were not counted for the purpose of the present analysis. AF recurrence was defined as a documented episode of any atrial arrhythmias (AF, AT and atrial flutter) lasting ≥ 30 s during the follow-up period after a blanking period of 3 months[20]. Patient's follow-up was terminated at the first AF episode recorded after the blanking period.

Statistical Analysis

The statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The count data was represented by a composition ratio, and the comparison between the rates of the groups was performed by a chi-square test or an accurate probability method. The measurements were expressed as mean ± standard deviation, and the measurements of skewed distribution were expressed by Median (Q1-Q3). For continuous variables, *t*-test (parametric) and Mann Whitney U test (non-parametric) were used for comparison between groups. The variables with $p \leq 0.05$ in the univariate analysis were classified into the multivariate logistic regression model, and the multivariate logistic regression model was used to determine the independent risk factors for recurrence of CPVA in patients with PAF. The ROC curves of AF recurrence predicted by BNP and LA functional indicators were plotted, and the cut-off value and area under the curve (AUC) were determined. The test efficiency of each parameter was analyzed. Multivariate pipeline regression analysis was used to test the relationship between LA function and BNP. The difference was statistically significant with $p \leq 0.05$.

Results

Comparison of Clinical Data

Two hundred forty-three patients underwent TEE before the operation. Ten patients were not treated with CPVA due to heart rhythm, left atrial appendage thrombosis, SEC or low LAAV (less than 40cm/s). The remaining 233 patients were successfully treated with CPVA, with an average age of 63.1±9.3 years (range, 39-75 years; male: female =195: 38). All patients were recorded sinus rhythm after the operation in digital subtraction angiography (DSA). Two hundred thirty-three patients were observed and followed up 3-6 months after CPVA. According to a documented episode of any atrial arrhythmias (AF, AT and atrial flutter) lasting ≥ 30 s during and the monthly 24 hours dynamic electrocardiogram after a blanking period of 3 months, the patients were divided into AF Recurrence Group (n = 42) and Sinus Rhythm Group (n = 191). The mean follow-up period of AF Recurrence Group and Sinus Rhythm Group were 4 (3, 5) months and 6 (6, 6) months (Figure 1). The clinical data of the patients were shown in Table I. Compared with the Sinus Rhythm Group, the Recurrence Group had a long course of AF, and the BNP in the Recurrence Group is higher than the Sinus Rhythm Group (all $p<0.01$).

Difference in Left Atrial Volume and Function

Before CPVA, LAVImin and LAVIpre-a of the Recurrence Group were higher than the Sinus Rhythm Group (all $p=0.001$). Expansion index, DEI, PEI, and AEI of the Recurrence Group were significantly lower than those of the Sinus Rhythm Group (all $p=0.001$) (Figure 2, Table II).

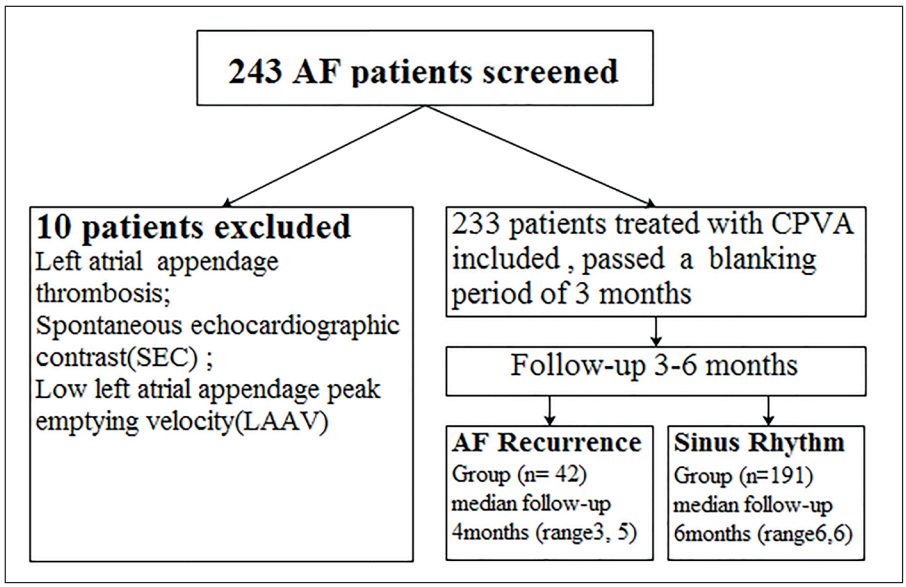

Figure 1. Study population, selection, and follow-up.

Independent Risk Factors for AF Recurrence

Adjusting for age, sex, LAVImin, LAVIpre-a, expansion index, PEI and AEI, multivariate logistic regression analysis showed that preoperative DEI, BNP, and AF duration were the independent risk factors for AF recurrence after 3 months of CPVA (*p*-range=0.001-0.016) (Table III).

Table I. Clinical data of the 233 PAF patients before CPVA.

	Recurrence Group n = 42	Sinus Rhythm Group n = 191	t or χ^2	*p*
Age (years old)	60.92±10.47	64.04±9.05	0.288	0.078
BMI (kg/m^2)	23.44±3.75	23.74±2.89	0.075	0.626
female, n (%)	5 (11.90)	33 (17.28)	0.153	0.493
History of AF (month)	9.3±4.6	7.4±3.8	0.450	0.005
Family history of AF, n (%)	7 (16.67)	18 (9.42)	1.178	0.176
Rhythm control drugs, n (%)	24 (57.14)	105 (54.97)	0.007	0.933
Prior hospitalization for AF, n (%)	12 (28.57)	34 (17.80)	1.887	0.170
Hypertension, n (%)	11 (26.19)	44 (23.04)	0.055	0.814
Diabetes mellitus, n (%)	12 (28.57)	43 (22.51)	0.405	0.525
Hypercholesterolemia, n (%)	8 (19.05)	27 (14.14)	0.147	0.474
Obstructive sleep apnea, n (%)	4 (9.52)	14 (7.33)	0.027	0.871
Drink, n (%)	7 (16.67)	36 (18.85)	0.309	0.829
Vascular disease, n (%)	5 (11.90)	15 (7.85)	0.296	0.586
History of stroke or TIA, n (%)	6 (14.29)	16 (8.37)	0.029	0.239
CHADS2	1.0 (0, 1.0)	1.0 (0, 1.0)	0.004	0.983
CHADS2-Vasc	1.0 (1, 0,3.0)	1.0 (1.0, 2.0)	0.023	0.887
Heart rate (beat/min)	79 (64.3, 91.0)	78 (63, 92.0)	0.081	0.637
Serum creatinine (umol/l)	63.04 ±13.26	61.07± 18.19	0.125	0.503
LAAV (cm/s)	60.27±11.37	57.76±11.03	1.320	0.188
BNP (pg/ml)	530.5 (380.3, 673.3)	278.2 (194.0, 438.2)	0.876	0.001

Footnote: BMI, body mass index; TIA, transient cerebral ischemic attacks; CHADS2, CHADS2-Vasc are stroke risk scores in patients with AF; LAAV, left atrial appendage peak emptying velocity.

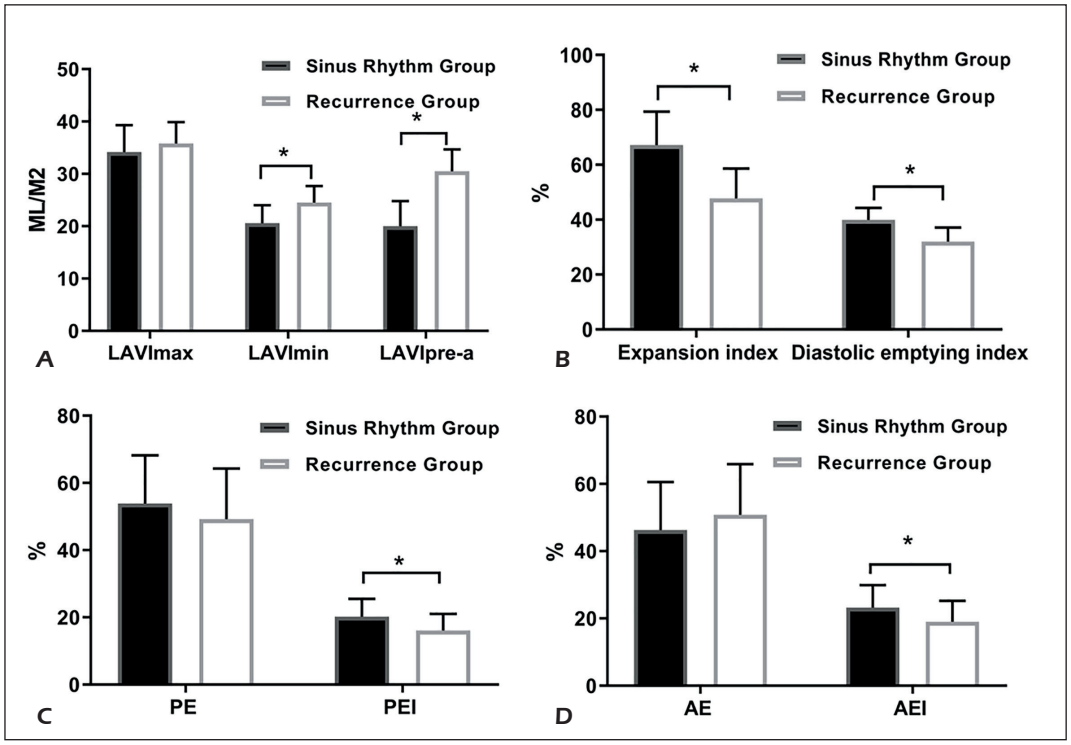

Figure 2. The comparisons of LA volume (**A**), and LA reservoir (**B**), conduit (**C**) and booster pump (**D**) function before CVPA in the Sinus Rhythm Group and the Recurrence Group. AE, active emptying percentage of total emptying; AEI, active emptying index; PE, passive emptying percentage of total emptying; PEI, passive emptying index. *indicates $p<0.05$.

ROC Curve

The ROC curves of the LAVImax, DEI, BNP, and DEI combined with BNP to predict the AF recurrence were shown in Table IV and Figure 3. The AUC of predicted recurrence of BNP, DEI and combined indicators were compared with LAVImax, respectively. The z statistics were 2.497 (95% CI: 0.028 to 0.236, $p=0.013$), 5.274 (95% CI: 0.170 to 0.371, $p<0.001$), and 5.730 (95% CI: 0.193 to 0.391, $p<0.001$). The z statistics of the AUC of the joint index, BNP+DEI, to predict AF recurrence was 1.420

Table II. Comparison of LA volume and function in 233 PAF patients before CPVA.

	Recurrence Group n = 42	Sinus Rhythm Group n = 191	t or χ^2	*p*
LVEF (%)	56.0 (51.0, 59.6)	56.0 (51.0, 60.0)	0.110	0.602
LAVI max (ml/m2)	35.81±4.12	34.2±5.14	0.334	0.067
LAVI min (ml/m2)	24.53±3.21	20.65±3.46	1.185	0.001
LAVI pre-a (ml/m2)	30.52±4.23	27.08±4.83	0.780	0.001
Expansion index (%)	47.84±10.84	67.24±12.2	1.680	0.001
DEI (%)	32.07±5.19	39.94±4.36	1.672	0.001
PE (%)	49.24±15.18	53.98±14.34	0.322	0.057
PEI (%)	16.13±4.95	20.24±5.31	0.797	0.001
AE (%)	50.83±15.16	46.38±14.36	0.322	0.057
AEI (%)	19.02±6.26	23.28±6.71	3.368	0.001

Footnote: LVEF, left ventricular ejection fractions; BNP, brain natriuretic peptide; LAVI max, left atrial maximum volume index; LAVI min, left atrial minimum volume index; LAVI pre-a, left atrial volume index before contraction; DEI,diastolic emptying index; PE, passive emptying percentage of total emptying; PEI, passive emptying index; AE, active emptying percentage of total emptying; AEI, active emptying index.

Table III. Univariate and mutivariate analyses of factors affecting AF recurrence.

	Univariate logistic regression			Multivariate logistic regression		
	p	OR	95% CI	*p*	OR	95% CI
Age (years old)	0.080	0.969	0.94, 1,01	0.609	0.986	0.93, 1.04
Sex %	0.396	0.647	0.24, 1.77	0.968	0.974	0.27, 3.57
History of AF (month)	0.007	1.120	1.03, 1.22	0.016	1.154	1.03, 1.30
BNP (pg/ml)	0.001	1.003	1.01, 1.04	0.001	1.004	1.01, 1.07
LAVI min (ml/m^2)	0.001	1.348	1.21, 1.51	0.137	3.666	0.66, 20.27
LAVI pre-a (ml/m^2)	0.001	1.155	1.07, 1.24	0.475	1.345	0.60, 3.04
Expansion index (%)	0.001	0.853	0.81, 0.90	0.111	0.850	0.70, 1.04
DEI (%)	0.001	0.683	0.61, 0.77	0.001	0.655	0.57, 0.75
PEI (%)	0.001	0.852	0.79, 0.92	0.488	0.942	0.80, 1.12

Footnote: BNP, brain natriuretic peptide; LAVI min, left atrial minimum volume index; LAVI pre-a, left atrial volume index before contraction; DEI, diastolic emptying index; PEI, passive emptying index; AEI, active emptying index.

(95% CI: -0.008 to 0.051, p=0.156), compared with that of the single factor DEI.

Discussion

The treatment of PAF has made significant progress, and catheter ablation has become an irreplaceable treatment; what is more, continued use of ADT significantly reduces the recurrence of atrial tachyarrhythmia after CPVA[5]. However, radical transcatheter interventions can elicit the fibrosis which propitiate the creation of arrhythmogenic scars, furthermore, pulmonary vein stenosis is an important complication after catheter ablation[1]. The benefits of ablation are often offset by the recurrence of AF. Therefore, identifying high-risk AF patients with non-invasive indicators may help doctors make better choices. In the present study, RT-3DE was used to evaluate LA volumes and function in PAF patients treated with CPVA, RT-3DE coupled with a fully automated endocardial contouring algorithm to measure volumes and EF is feasible, accurate, and reproducible. It is now possible to measure 3D volumes and EF in patients accurately and rapidly compared with CMR. The implementation of such an automated workflow may promote wider use in routine clinical practice[19].

Patients with PAF suffer from recurrent AF rhythm, loss of effective atrial contraction, and increased LA volume and pressure load. Conversion of atrial fibrillation to sinus rhythm also results in a transient mechanical dysfunction of atrium, termed atrial stunning, which may show LA or left atrial appendage thrombosis, SEC or low LAAV[21]. All images and blood were collected in sinus rhythm, and LAAC velocity was used to exclude left atrial stunning. Left atrial remodeling is mainly due to the development of atrial tachyarrhythmias or the alteration in atrial structure secondary to pressure or volume overload[22]. The occurrence of AF is a gradual process, and when PAF patients develop significant structural remodeling, it usually indicates irreversible microscopic changes and a more severe disease phenotype. In recent years, studies have shown that the degree of preoperative LA reconstruction plays an essential role in the success of CPVA. The PAF patients selected in this study were mostly in the

Table IV. Evaluation of the power of the BNP and DEI before CPVA of predicting AF recurrence by ROC curve.

	Criterion	AUC	95% CI	Sensitivity (%)	Specificity (%)
LAVI max (ml/m^2)	50.3	0.601	0.566 to 0.694	76.19	49.74
DEI (%)	36.67	0.887	0.828 to 0.922	90.48	79.06
BNP (pg/ml)	432	0.749	0.688 to 0.803	73.81	74.35
BNP (pg/ml) + DEI (%)	≥ 432 and ≤ 36.67	0.908	0.863 to 0.942	80.95	90.05

Footnote: BNP, B-type natriuretic peptide; DEI, Diastolic emptying index; CPVA, circumferential pulmonary vein ablation.

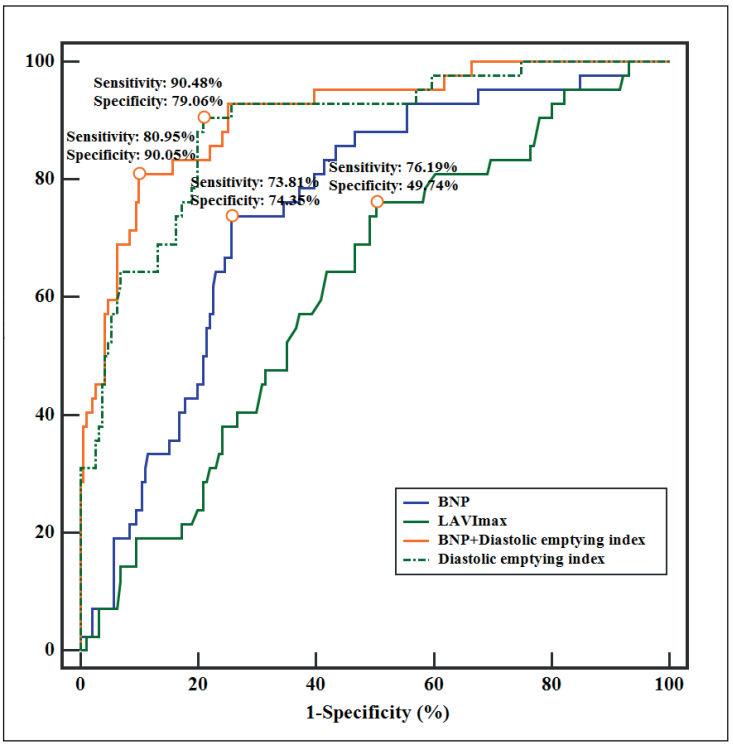

Figure 3. The Receiver Operator Curve (ROC) for the ability of LAVImax, BNP and diastolic emptying index (DEI) to discriminate patients with or without the recurrence of PAF after CPVA.

early stage of AF. The LA volume of the patients was normal or slightly increased and the ejection fraction was still within the normal range. There was no significant difference in LAVImax between the Recurrence Group and the Sinus Rhythm group, while the 3D analysis of LA function in these patients will have a more substantial impact on their prognosis[23]. The biological blood indicator BNP is released when the myocardium is stretched and the wall stress increases[13,24]. In AF patients with normal cardiac function, the BNP gene expression is enriched in atrium[10], they may be the ultrasound-structural and hematological indicator of wall stress.

In the early stage of AF, the contractile and structural remodeling may be reversible, but with the increased number of attacks and extended attack time, it is difficult to reverse the progress, which is called the "AF-promoting AF" mechanism[25]. PAF has a chronic tendency. LA remodeling is an adaptation to the LA progression over time. Therefore, it is essential to assess the patient's medical benefit before surgery. Unlike the previous study, which proposed that "LA enlargement is a powerful predictor of AF recurrence"[26], in this study we found that the DEI of the patients with PAF is an independent risk factor for predicting AF recurrence after CVPA, and the ROC curve showed that combined with BNP, the sensitivity and specificity of the prediction could reach 80.95% and 90.05%, indicating that stress/capacity-overload-induced structural remodeling and neurohumoral changes play a vital role in AF recurrence. In the early stage of AF episode, the atrium may increase its ejection capacity by increasing the preload (Frank-Starling mechanism), as seen in an increase in volume. However, its ability to expand is limited, with frequent attacks, LA results in microscopic myocardial fibrosis and macroscopic volume expansion and contraction remodeling, leading to irreversible changes in LA function. In this study, we found that the risk of recurrence of patients with decreased LA reservoir function was increased, indicating that the LA reservoir function, as a predictor of recurrence at this stage, may reflect the degree of remodeling in patients with PAF. LA stress analysis demonstrated that LA reservoir function could predict the AF recurrence after CPVA[27]. Habibi et al[28] have also shown that LA reservoir function measured with cardiac magnetic resonance can additionally increase the risk of recurrence.

BNP is also an independent risk factor for predicting AF recurrence after CVPA. Recurrent patients show an increase in BNP before surgery, and patients with symptomatic PAF have a moderate rise in BNP. A decrease in plasma BNP con-

centration may indicate the success of operation shortly after ablation[29]. The decline in BNP levels may be associated with early recovery of cardiac function and subsequent maintenance of sinus rhythm, but postoperative BNP recovery is slower than volume improvement[30]. Also, low BNP levels are associated with sinus rhythm maintenance after AF cardioversion, and the baseline BNP level may be a predictor of recurrence after successful cardioversion[31]. Silvet et al[32] also found that the elevated BNP levels after atrial volume/pressure overload were closely associated with AF persistence. Besides, BNP increases the occurrence of atrial arrhythmia of pulmonary vein origin[33], increased level of BNP is associated with larger left atrial size, which could result in higher risk of post-ablation AF recurrence due to atrial fibrosis and remodeling[34]. BNP may inhibit cardiac sympathetic activity and enhance vagal activity through the cGMP pathway, which leads to arrhythmias, ultimately AF recurrence[35].

The incremental predictive power of the left atrial reservoir function combined with BNP in this study has not yet reached statistical significance. Although the increase in LA is associated with an increase in BNP, LA expansion is preceded or early in the onset of AF and is a persistent factor that does not accurately reflect the trend of BNP fluctuations. Abnormal LA function in patients with AF is an essential factor affecting BNP secretion. Future research will provide a new perspective for the mechanism of recurrence of PAF through the study of the correlation between LA function and BNP.

Combination of non-invasive RT-3DE imaging technology and the critical biomarker identifies patients with high-risk recurrence among the PAF with CPVA. Evaluating the risk of AF recurrence after ablation by left atrial function and myocardial stretch, which provides valuable information for clinically determining whether radiofrequency ablation is needed, as well as ablation strategies and postoperative maintenance of sinus rhythm-related treatment. It should be noted that the LA function obtained by the RT-3DE and BNP level may be indirect measures of myocardial wall stress. Future studies should evaluate the relationship between wall stress and postoperative recurrence based on invasive measurement.

Conclusions

In patients with PAF treated with CPVA, the impaired DEI of LA reservoir function and increased BNP level may serve as useful predictors of PAF recurrence.

Trial Registration

The present study was retrospectively registered in the Chinese Clinical Trial Registry, A Primary Registry of the International Clinical Trial Registry Platform, World Health Organization (Registration No: ChiCTR1900021658). The registered date was March 3, 2019.

Funding

This work was supported by Natural Science Foundation of China (Grant No. 81471690); Application Basic Project of Changzhou City Health Bureau (Grant No. CJ20190086). Application Basic Project of Changzhou City Health Bureau (Grant No. WZ201804).

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893-2962.

2) Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee K L, Packer DL. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: The CABANA Randomized Clinical Trial. JAMA 2019; 321: 1275-1285.

3) Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010; 303: 333-340.

4) Mansour M, Heist EK, Agarwal R, Bunch TJ, Karst E, Ruskin JN, Mahapatra S. Stroke and cardiovascular events after ablation or antiarrhythmic drugs for treatment of patients with atrial fibrillation. Am J Cardiol 2018; 121: 1192-1199.

5) Duytschaever M, Demolder A, Phlips T, Sarkozy A, El Haddad M, Taghji P, Knecht S, Tavernier R, Vandekerckhove Y, De Potter T. Pulmonary vein isolation with vs. without continued antiarrhythmic drug treatment in subjects with recurrent atrial fibrillation

(POWDER AF): results from a multicentre randomized trial. Eur Heart J 2018; 39: 1429-1437.

6) Pokorney SD, Daubert JP. Atrial fibrillation ablation alone or atrial fibrillation ablation plus an antiarrhythmic drug? Eur Heart J 2018; 39: 1438-1441.

7) Anselmino M, Gili S, Castagno D, Ferraris F, Matta M, Rovera C, Giustetto C, Gaita F. Do left atrial appendage morphology and function help predict thromboembolic risk in atrial fibrillation? J Cardiovasc Med (Hagerstown) 2016; 17: 169-176.

8) Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol 2008; 1: 62-73.

9) Rohner A, Brinkert M, Kawel N, Buechel R R, Leibundgut G, Grize L, Kuhne M, Bremerich J, Kaufmann B A, Zellweger M J, Buser P, Osswald S, Handke M. Functional assessment of the left atrium by real-time three-dimensional echocardiography using a novel dedicated analysis tool: initial validation studies in comparison with computed tomography. Eur J Echocardiogr 2011; 12: 497-505.

10) Tuinenburg AE, Brundel BJ, Van Gelder IC, Henning RH, Van Den Berg MP, Driessen C, Grandjean JG, Van Gilst WH, Crijns HJ. Gene expression of the natriuretic peptide system in atrial tissue of patients with paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 1999; 10: 827-835.

11) D'Souza SP, Davis M, Baxter GF. Autocrine and paracrine actions of natriuretic peptides in the heart. Pharmacol Ther 2004; 101: 113-129.

12) Zhang Y, Chen A, Song L, Li M, Chen Y, He B. Association between baseline natriuretic peptides and atrial fibrillation recurrence after catheter ablation. Int Heart J 2016; 57: 183-189.

13) Hall C. NT-ProBNP: the mechanism behind the marker. J Card Fail 2005; 11: S81-83.

14) Hopkins WE, Chen Z, Fukagawa NK, Hall C, Knot HJ, LeWinter MM. Increased atrial and brain natriuretic peptides in adults with cyanotic congenital heart disease: enhanced understanding of the relationship between hypoxia and natriuretic peptide secretion. Circulation 2004; 109: 2872-2877.13.

15) Mueller C, McDonald K, de Boer R A, Maisel A, Cleland J G F, Kozhuharov N, Coats A J S, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL, Jr. Heart Failure Association of the European Society of Cardiology Practical Guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019; 21: 715-731.

16) Prontera C, Zaninotto M, Giovannini S, Zucchelli G C, Pilo A, Sciacovelli L, Plebani M, Clerico A. Proficiency testing project for brain natriuretic peptide (BNP) and the N-terminal part of the propeptide of BNP (NT-proBNP) immunoassays: the CardioOrmocheck study. Clin Chem Lab Med 2009; 47: 762-768.

17) York MK, Gupta DK, Reynolds CF, Farber-Eger E, Wells QS, Bachmann KN, Xu M, Harrell FE, Jr., Wang TJ. B-type natriuretic peptide levels and mortality in patients with and without heart failure. J Am Coll Cardiol 2018; 71: 2079-2088.

18) Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, Lederlin M, Mondillo S, Edvardsen T, Sitges M, Grapsa J, Garbi M, Senior R, Gimelli A, Potpara TS, Van Gelder IC, Gorenek B, Mabo P, Lancellotti P, Kuck KH, Popescu BA, Hindricks G, Habib G, Cardim NM, Cosyns B, Delgado V, Haugaa K H, Muraru D, Nieman K, Boriani G, Cohen A. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging 2016; 17: 355-383.

19) Thavendiranathan P, Liu S, Verhaert D, Calleja A, Nitinunu A, Van Houten T, De Michelis N, Simonetti O, Rajagopalan S, Ryan T, Vannan MA. Feasibility, accuracy, and reproducibility of real-time full-volume 3D transthoracic echocardiography to measure LV volumes and systolic function: a fully automated endocardial contouring algorithm in sinus rhythm and atrial fibrillation. JACC Cardiovasc Imaging 2012; 5: 239-251.

20) Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, Natasja de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace 2018; 20: e1-e160.

21) Khan I A. Atrial stunning: basics and clinical considerations. Int J Cardiol 2003; 92: 113-128.

22) Thomas L, Abhayaratna W P. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. JACC Cardiovasc Imaging 2017; 10: 65-77.

23) Miyasaka Y, Tsujimoto S, Maeba H, Yuasa F, Takehana K, Dote K, Iwasaka T. Left atrial volume by real-time three-dimensional echocardiography: validation by 64-slice multidetector computed tomography. J Am Soc Echocardiogr 2011; 24: 680-686.

24) Gaborit F, Bosselmann H, Tonder N, Iversen K, Kumler T, Kistorp C, Soletormos G, Goetze JP, Schou M. Association between left ventricular global longitudinal strain and natriuretic peptides in outpatients with chronic systolic heart failure. BMC Cardiovasc Dis 2015; 15: 92-99.

25) Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92: 1954-1968.

26) Fornengo C, Antolini M, Frea S, Gallo C, Grosso Marra W, Morello M, Gaita F. Prediction of atrial fibrillation recurrence after cardioversion in patients with left-atrial dilation. Eur Heart J Cardiovasc Imaging 2015; 16: 335-341.

27) Mirza M, Caracciolo G, Khan U, Mori N, Saha S K, Srivathsan K, Altemose G, Scott L, Sengupta P, Jahangir A. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. Journal of interventional cardiac electrophysiology. J Interv Card Electrophysiol 2011; 31: 197-206.

28) Habibi M, Lima JA, Gucuk Ipek E, Zimmerman SL, Zipunnikov V, Spragg D, Ashikaga H, Rickard J, Marine JE, Berger RD, Calkins H, Nazarian S. The association of baseline left atrial structure and function measured with cardiac magnetic resonance and pulmonary vein isolation outcome in patients with drug-refractory atrial fibrillation. Heart Rhythm 2016; 13: 1037-1044.

29) Gould PA, Gula LJ, Bhayana V, Subbiah RN, Bentley C, Yee R, Klein GJ, Krahn AD, Skanes AC. Characterization of cardiac brain natriuretic peptide release in patients with paroxysmal atrial fibrillation undergoing left atrial ablation. Circ Arrhythm Electrophysiol 2010; 3: 18-23.

30) Bernard-Brunet A, Saint Etienne C, Piver E, Zannad N, Pages J C, Fauchier L, Babuty D. Incomplete recovery of mechanical and endocrine left atrial functions one month after electrical cardioversion for persistent atrial fibrillation: a pilot study. J Translat Med 2014; 12: 51-58.

31) Xu X, Tang Y. Relationship between brain natriuretic peptide and recurrence of atrial fibrillation after successful electrical cardioversion: an updated meta-analysis. Braz J Cardiovasc Surg 2017; 32: 530-535.

32) Silvet H, Young-Xu Y, Walleigh D, Ravid S. Brain natriuretic peptide is elevated in outpatients with atrial fibrillation. Am J Cardiol 2003; 92: 1124-1127.

33) Lin YK, Chen YC, Chen YA, Yeh YH, Chen SA, Chen YJ. B-type natriuretic peptide modulates pulmonary vein arrhythmogenesis: a novel potential contributor to the genesis of atrial tachyarrhythmia in heart failure. J Cardiovasc Electrophysiol 2016; 27: 1462-1471.

34) Jiang H, Wang W, Wang C, Xie X, Hou Y. Association of pre-ablation level of potential blood markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. Europace 2017; 19: 392-400.

35) Herring N, Zaman JA, Paterson DJ. Natriuretic peptides like NO facilitate cardiac vagal neurotransmission and bradycardia via a cGMP pathway. Am J Physiol Heart Circ Physiol 2001; 281: H2318-2327.