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Original Article

Red blood cell distribution width intimately correlated with clinical recurrence of atrial fibrillation after catheter ablation

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Abstract: Purpose: Red blood cell distribution width was demonstrated to be relevant to the incidence of atrial fibrillation in general population and new-onset patients who underwent coronary artery bypass grafting. Current study aimed to investigate the correlation between them following catheter ablation. Significant findings: Early recurrence of atrial fibrillation developed in 53 (24.2%) patients. There was a significant lower incidence of late recurrence of atrial fibrillation in patients who had no early recurrence of atrial fibrillation (24/166, 14.5%) compared with those who experienced early recurrence of atrial fibrillation (44/53, 83%). Left atrium diameter (HR 1.18, 95% CI 1.10-1.26, $P < 0.001$), pulmonary vein isolation (HR 0.15, 95% CI 0.02-0.97, $P = 0.047$), and red blood cell distribution width (HR 4.29, 95% CI 2.17-8.46, $P < 0.001$) were independent predictors for early recurrence of atrial fibrillation while left atrium diameter (HR 1.14, 95% CI 1.05-1.23, $P = 0.036$), red blood cell distribution width (HR 5.73, 95% CI 2.78-11.77, $P < 0.001$) and early recurrence of atrial fibrillation (HR 9.28, 95% CI 3.79-22.68, $P < 0.001$) were independent predictors for late recurrence of atrial fibrillation. Conclusions: Red blood cell distribution width is a predictor for early/late recurrence of atrial fibrillation following catheter ablation.

Keywords: Red blood cell distribution width, catheter ablation, atrial fibrillation recurrence

Introduction

As the most common cardiac arrhythmia, atrial fibrillation (AF) is tightly associated with the high risk of cardiovascular events, for instance, ischemic stroke [1]. Catheter ablation (CA) was recently established as a curative therapy for paroxysmal/persistent AF. Whereas, successful CA could also generate AF in 15%-40% patients who will receive CA later [2-4]. Several clinical and imaging parameters were predictors for AF recurrence after CA, for instance, hypertension, long duration of AF, enlarged left atrium diameter (LAD), elevated left atrium volume (LAV) and declined left atrium function (LAF) [5-8]. Furthermore, mounting clinical and experimental evidences indicated a link between post-ablation AF recurrence and inflammation [9-12], take baseline C-reactive protein (CRP) which is an inflammatory marker, as an example, it predicted early recurrence of AF (ERAF) as well as late recurrence of AF (LRAF) after ablation [13, 14].

As a numerical measure of circulating erythrocyte, red blood cell distribution width (RDW) was delineated to be an important predictor to adverse outcomes in general population and patients' cardiovascular morbidity and mortality who suffered myocardial infarction ever [15, 16]. Moreover, RDW was illuminated to be tightly correlated with AF incidence in both general population and new-onset patients after coronary artery bypass grafting [17, 18].

However, to the best of our knowledge, there was no study on the role of RDW in prediction of post-ablation AF recurrence to date. Therefore, current study aimed to investigate the relationship between RDW and AF recurrence after CA.

Materials and methods

Participants

We retrospectively reviewed 219 consecutive patients (59.08±8.16 years, 139 males and 80 females) who underwent first-time left atrial CA

Table 1. Baseline demography and Characteristics of study population

Characteristics	N (%)
Patients	219
Age (years)	59.08±8.16
Male, n (%)	139 (63.5%)
Female, n (%)	80 (36.5%)
Type of AF	
Paroxysmal AF	144 (65.8%)
Persistent AF	75 (34.2%)
Echocardiography	
LAD (mm)	41.69±7.28
LVEDD (mm)	46.35+5.03
LVEF (%)	61.26±4.29

(LACA) for documented AF between July 2013 and August 2014 in the first affiliated hospital of Zhengzhou University. All of them burdened with symptomatic paroxysmal or persistent AF and manifested no response to at least one anti-arrhythmic drug (AADs) previously. Paroxysmal AF was defined as self-termination of AF episodes within 7 days while persistent AF defined as duration of AF episodes > 7 days or termination assisted by cardioversion [19].

Patients who suffered from moderate-to-severe valvular disease, concomitant inflammatory diseases, thrombus in left atrium, renal dysfunction, thyroid dysfunction, hepatic and haemolytic disorders, neoplastic diseases or any other systemic disorders were excluded. Prior written and informed consent were obtained from each patient, current study was approved by Institutional Ethics Committee.

Baseline examinations

Demographic and clinical data were collected from patients' medical records. In all patients, transthoracic and transesophageal echocardiography was performed prior to CA. LAD as well as left ventricular ejection fraction (LVEF) was determined utilizing standard measurements. Complete blood count and biochemical values were evaluated from blood samples obtained by antecubital vein puncture in the hematology laboratory of our institution.

LACA

LACA was performed as previously elaborated [20]. Briefly, blood pressure and oxygen saturation were monitored when patients were under conscious sedation. Left atrium was explored using trans-septal approach. Left atrial geometry was reconstructed with ablation catheter (Navi-Star Thermo Cool, Biosense-Webster, USA) whose tip was 3.5 mm in the CARTO system. In all patients, circumferential left atrial ablation lines were placed around the antrum of ipsilateral pulmonary veins (PVs), under the temperature of 43°C, maximum power at 35 W and infusion rate at 17 mL/min. In patients with persistent AF, additional linear lesions were added to the left atrial roof/isthmus. The tricuspid isthmus which was responsible for tachycardia was identified and ablated when a typical atrial flutter had been documented before conducting the procedure. Ablation of complex fractionated electrograms was not performed. The endpoints of electrical isolation in all PVs and left atrial isthmus block were defined by bidirectional pacing. Bidirectional block of roof lines was confirmed by differential pacing from left atrium appendage vs. left atrium posterior wall [21].

Post-ablation management and follow-up

Regarding there were neither contraindications nor intolerance in patients, all of them received AADs. The AAD treatment discontinued when atrial tachyarrhythmia did not recur 3 months later. All asymptomatic patients were followed up by a 12-lead electrocardiogram (ECG) and 24 h Holter recording. Patients obtained an ECG registration when experiencing palpitations. AF recurrence was defined as any recording of AF or atrial flutter on ECG or an episode longer than 30 s on 24 h Holter recording. When AF recurred, sinus rhythm was restored by transthoracic cardioversion or intravenous administration of AADs. In the present study, ERAF was defined as recurrence of AF within 3 months following CA while LRAF defined as recurrence of AF 3 months after the procedure.

Statistical analysis

Data were analyzed by SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) and expressed as the mean ± standard deviation (SD), meanwhile, all of the categorical data are showed as percentages. Comparisons were carried out by independent Student's *t*, Fisher exact, Mann-Whitney rank-sum or chi-square tests when

Table 2. Characteristics of patients in ERAF+ and ERAF- groups (n = 219)

Variables	ERAF- (n = 166)	ERAF+ (n = 53)	*P* value
Age (years)	59.03±8.69	59.23±6.30	0.879
Male n (%)	104 (62.65)	35 (66.04)	0.656
Persistent AF n (%)	54 (32.53)	37 (69.81)	< 0.001
Diabetes mellitus n (%)	15 (9.04)	2 (3.77)	0.214
Hypertension n (%)	57 (34.34)	18 (33.96)	0.960
Heart failure n (%)	4 (2.41)	4 (7.55)	0.083
LAD (mm)	35.53±5.43	42.53±7.24	< 0.001
LVEDD (mm)	46.24±4.01	47.98±6.58	0.021
LVEF (%)	61.84±3.95	60.57±5.46	0.065
RDW (%)	13.22±0.56	14.17±0.49	< 0.001
Hemoglobin (g/L)	137.13±13.43	137.66±12.11	0.797
PVI n (%)	164 (98.80)	49 (92.45)	0.014
ACEI/ARB n (%)	63(37.95)	24 (45.28)	0.343
β-blockers n (%)	89 (53.61)	31 (58.49)	0.535
Amiodarone n (%)	144 (86.75)	50 (94.34)	0.131
Class IC AADs n (%)	10 (6.02)	1 (1.89)	0.231
Follow-up (months)	18 (5-18)	18 (5-18)	0.861
ERAF n (%)	-	-	-

Table 3. Characteristics of patients in LRAF+ and LRAF- groups (n = 219)

Variables	LRAF- (n = 151)	LRAF+ (n = 68)	*P* value
Age (years)	58.99±8.94	59.26±6.16	0.821
Male n (%)	98 (64.90)	41 (60.29)	0.513
Persistent AF n (%)	53 (35.10)	38(55.88)	0.004
Diabetes mellitus n (%)	14 (9.27)	3 (4.41)	0.215
Hypertension n (%)	54 (35.76)	21 (30.88)	0.482
Heart failure n (%)	4 (2.65)	4 (5.88)	0.238
LAD (mm)	35.32±4.97	41.44±7.82	< 0.001
LVEDD (mm)	46.36±4.04	47.34±6.14	0.162
LVEF (%)	61.78±3.98	60.99±5.15	0.214
RDW (%)	13.16±0.50	14.07±0.38	< 0.001
Hemoglobin (g/L)	137.87±13.83	135.88±11.29	0.299
Pulmonary vein isolation n (%)	149 (98.68)	64 (94.12)	0.056
ACEI/ARB n (%)	60 (39.74)	27 (39.71)	0.997
β-blockers n (%)	83 (54.97)	37 (54.41)	0.939
Amiodarone n (%)	131 (86.75)	63 (92.64)	0.206
Class IC AADs n (%)	9 (5.96)	2 (2.94)	0.345
Follow-up (months)	18 (5-18)	18 (5-18)	0.566
ERAF n (%)	9 (5.96)	44 (64.71)	< 0.001

ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

appropriate. Variables whose *P*-values that less than 0.10 in the univariate analysis were candidates for binary logistic regression analysis, which were finally determined in a forward stepwise variable selection procedure. *P*-values that less than 0.05 were used to assess significant differences.

Results

Baseline demography and characteristics of the participants

A total of 219 patients (59.08±8.16 years, 139 males and 80 females) were involved in current study. Of them, there were 144 (65.8%) patients displayed paroxysmal AF, however, the remaining 75 (34.2%) manifested persistent AF as shown in **Table 1**.

Characteristics of patients in ERAF+ and ERAF- groups

After a median 18-month follow-up time, ERAF was developed in 53 (24.2%) patients. As presented in **Table 2**, patients with ERAF displayed higher RDW levels, greater LAD and left ventricular end-diastolic dimension (LVEDD), higher rate of persistent AF and lower rate of PVI in comparison with patients who remained in sinus rhythm. However, no significant differences were found in patients between ERAF+ and ERAF- groups regarding age, gender, LVEF and hemoglobin. The prevalence of diabetes mellitus, heart failure, hypertension as well as medication use (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, amiodarone and class IC antiarrhythmic drugs, *β*-blockers, AADs) demonstrated no predominant difference between the two groups.

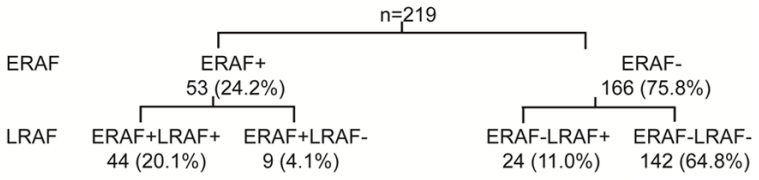

Figure 1. Long-term follow-up of ERAF+ and ERAF- groups.

Table 4. Independent variables related to ERAF and LRAF

Variables	HR	95% CI	*P* value
ERAF			
LAD	1.18	1.10-1.26	< 0.001
PVI	0.15	0.02-0.97	0.047
RDW	4.29	2.17-8.46	< 0.001
LRAF			
LAD	1.14	1.05-1.23	0.036
RDW	5.73	2.78-11.77	< 0.001
ERAF	9.28	3.79-22.68	< 0.001

Characteristics of patients in LRAF+ and LRAF- groups

ERAF was identified in 68 (31.1%) patients (**Table 3**). There were significant differences regarding RDW levels, LAD, rate of persistent AF and ERAF between the LRAF+ and LRAF- groups. Whereas, no significant difference was discovered between two groups regarding age, gender, LVEDD, LVEF, hemoglobin and the prevalence of diabetes mellitus, hypertension, pulmonary vein isolation, heart failure and medication use (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, amiodarone, class IC antiarrhythmic drugs and *β*-blockers).

Long-term follow-up of ERAF+ and ERAF- groups

There was a significant higher incidence of LRAF- in patients who were ERAF- (142 patients, 64.8%) in comparison with those who experienced ERAF ever (9 patients, 4.1%). LRAF+ was observed in a predominant larger number of patients who had experienced ERAF after CA (44 patients, 20.1%) than those who were ERAF- (24 patients, 11.0%). Forty-four of the 53 patients (83.0%) were ERAF+ experienced LRAF as well within 18 months (**Figure 1**).

Independent predictors for ERAF and LRAF following RFCA

A multivariate logistic regression analysis demonstrated that LAD (HR 1.18, 95% CI 1.10-1.26, $P < 0.001$), pulmonary vein isolation (PVI, HR 0.15, 95% CI 0.02-0.97, $P = 0.047$) and RDW level (HR 4.29, 95% CI 2.17-8.46, $P < 0.001$) were independent predictors for ERAF. AF type (paroxysmal or persistent), heart failure, LVEDD and LVEF were excluded as independent predictors of ERAF. Moreover, LAD (HR 1.14, 95% CI 1.05-1.23, $P = 0.036$), RDW level (HR 5.73, 95% CI 2.78-11.77, $P < 0.001$), and ERAF (HR 9.28, 95% CI 3.79-22.68, $P < 0.001$) were independent predictors of LRAF following CA (**Table 4**).

Discussion

Based on the retrospective analysis of 219 patients, we demonstrated that dramatically up-regulated RDW independently related with the promoted risk of not only ERAF but also LRAF. As far as we know, this is the first study investigating this relationship. ERAF and greater LAD were also discovered to be related with LRAF which were consistent with previous studies [22, 23].

The dominant findings are as follows: there was a significant higher incidence of LRAF- in patients who were ERAF- (142 patients, 64.8%) in comparison with those who experienced ERAF ever (9 patients, 4.1%). LRAF+ was observed in a predominant larger number of patients who had experienced ERAF after CA (44 patients, 20.1%) than those who were ERAF- (24 patients, 11.0%). In multivariate logistic regression analysis following CA, LAD, PVI and RDW were discovered to be independent predictors for ERAF while LAD, RDW and ERAF were independent predictors for LRAF.

In the past decades, ablation has been emerged as a momentous therapeutic option for AF. Nonetheless, after ablation, AF recurrence in a substantial number of patients remains a formidable challenge. Appropriate patient selection is essential for optimal outcome. Factors have been identified as predic-

tors of AF recurrence after CA, including AF type, inflammation, sleep apnoea, obesity, ascendant LAD, increased age, hypertension, left atrial fibrosis and ERAF [5, 8, 13, 14, 23, 24]. However, there is as yet no conclusive consensus achieved on account of study population heterogeneity, differences in follow-up period and type of AF and so on. In the present study, we suggested that RDW is a predictor for AF recurrence following CA.

Erythrocytes transport oxygen to tissues, participate in cardiovascular regulation via releasing extracellular nucleotides and mediators [25]. Erythrolysis is associated with increased release of free radicals [26], which are considered to be detrimental to heart. AF recurrence results from defects in heart erythrocyte, whereas, the correlation between AF recurrence and RDW remains elusive.

Several pathophysiological states, including oxidative stress and inflammation could reduce red blood cell (RBC) survival and elevate RDW. Furthermore, inflammation might also up-regulate RDW by modifying iron metabolism or suppressing the production of or response to erythropoietin [27]. Thus, RDW elevation indicated inflammation activation, which was demonstrated to play a pivotal role in AF development and maintenance [9, 28, 29]. Inflammation and oxidative stress share the similar mechanism, induce calcium overload and reduce sodium channels, meanwhile, there is structural remodeling via fibroblast proliferation, inflammation as well as apoptosis [30]. In a rapid atrial pacing model performed in canine, RDW was found to be associated with several biomarkers of oxidative stress and inflammation [31].

In accordance with the aforementioned hypotheses, we found that AF recurrence was related with both elevated RDW level and increased LAD, which was an indicator to advanced left atrium structure rebuilding. Thus, RDW may represent an exception to the adage that "there's no such thing as a free lunch", providing significant prognostic information without adding cost or complexity to CA for AF. Further large-scale, prospective studies needed to be performed to underpin its precise pathophysiologic and prognostic roles.

Disclosure of conflict of interest

None.

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