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Elevated Red Blood Cell Distribution Width Predicts Recurrence After Catheter Ablation for Atrial Fibrillation in Patients With Heart Failure

– Comparison With Non-Heart Failure Patients –

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Background: Elevated red blood cell distribution width (RDW) predicts poor prognosis in patients with cardiovascular diseases. However, little is known about the association between RDW and outcomes after catheter ablation of atrial fibrillation (AF).

Methods and Results: A total of 757 patients who underwent radiofrequency catheter ablation of AF were divided into heart failure (HF, n=79) and non-HF (n=678) groups; RDW was assessed as a predictor after catheter ablation in each. During a 22.3-month follow-up period, the baseline RDW in the HF group was greater in the recurrence group than in the non-recurrence group (14.5±2.0% vs. 13.5±0.9%, P=0.013). In contrast, no significant difference in RDW at baseline was found in the non-HF group between the recurrence and non-recurrence groups (13.3±0.8% vs. 13.2±0.8%, P=0.332, respectively). Multivariate analysis demonstrated that RDW (hazard ratio 1.20, 95% confidence interval 1.01–1.40, P=0.034) was an independent predictor of AF recurrence in the HF group. The cut-off values of RDW for the recurrence of AF and major adverse events in the HF group were 13.9% and 14.8%, respectively.

Conclusions: High RDW is an independent predictor for the recurrence of AF and major adverse events in patients with HF after catheter ablation. RDW is a potential noninvasive marker in AF patients complicated with HF. (*Circ J* 2016; **80:** 627–638)

Key Words: Atrial fibrillation; Catheter ablation; Heart failure; Red blood cell distribution width

Red blood cell distribution width (RDW) is a measurement parameter of the variability of circulating red blood cell size and is easily available as part of a standard complete blood cell count. Traditionally, RDW is used as a method of differential diagnosis of anemia etiology.[1] High RDW reflects an elevated reticulocyte level because of the possibility of iron deficiency, hemolytic anemia, or folate and vitamin B deficiency. Recently, several studies have reported that elevated RDW is a prognostic factor for mortality and major adverse events in patients with heart failure (HF) and cardiovascular disease.[2–6]

As for atrial fibrillation (AF), a common cardiovascular disease, previous reports similarly demonstrated significant relationships between AF incidence and elevated RDW for prognostic assessment in the general population and postoperative patients.[7,8] However, few data exist for the assessment of the relationship between RDW and outcomes in patients undergoing catheter ablation of AF. Recent studies with relatively small samples reported that an elevated RDW predicted a late recurrence of AF in patients undergoing cryoballoon-based ablation.[9,10] No data exist from large-sample studies to evaluate the association between RDW and outcomes after catheter ablation, and the details of the possible mechanism underlying the abovementioned association remain unknown.

The present study sought to examine the association between RDW and outcomes after radiofrequency catheter ablation (RFCA) for AF in a large sample. Because RDW is mainly reported as a prognostic parameter of mortality and morbidity in patients with HF, we focused on the outcomes in patients with HF who underwent RFCA of AF, compared with non-HF patients, and individually assessed RDW as a prognostic factor after CA in this study.

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Methods

Study Population

The study population was retrospectively recruited from a CA database at Nagoya University Hospital. The database was approved by the institutional ethical committee. Patients who underwent RFCA of AF for the first time between January 2009 and December 2014 were included in this study. All the patients were referred for CA because they were refractory to antiarrhythmic and rate-control drugs or could not be administered these drugs because of severe HF, side effects, or comorbidities. The indications for CA of AF complied with the latest guideline.[11] Exclusion criteria were: (1) insufficient examination results at baseline or loss to follow-up within 3 months after CA; (2) emergency CA of AF for hemodynamic instability, and decompensated HF; (3) severe renal dysfunction with estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73 m^2 at baseline; (4) history of CA or MAZE procedure; (5) development of a major complication resulting in discontinuation of the ablation procedure; and (6) abnormal thyroid function, severe anemia (hemoglobin <10.0 g/dl for men; <9.0 g/dl for women), hematological disease, liver cirrhosis, therapy affecting bone-marrow suppression, folate and vitamin B12 deficiency, history of recent blood transfusion, infection, hemorrhage events, and surgical operation. Patients with HF were defined as having a history of HF hospitalization or left ventricular ejection fraction (LVEF) ≤40% on baseline echocardiography.

Examination Course

Patients who were scheduled for CA were admitted the day before the procedure. Informed consent was given by all of the patients according to hospital guidelines. At admission, baseline blood testing, echocardiography, electrocardiography, and Holter examination were performed. Antiarrhythmic agents were stopped 5 half-lives before ablation, except for amiodarone and bepridil, which were stopped >1 week before the procedure. Transesophageal echocardiography was performed in all patients to confirm the absence of atrial thrombus. Anticoagulant drugs, including novel anticoagulant agents, were continued during the procedure, as previously reported.[12]

Ablation Procedure

In the ablation procedure, vascular access was obtained via the right and left femoral and left subclavian veins. We also accessed the right femoral artery to perform coronary angiography and monitor blood pressure. After transseptal puncture using intracardiac echocardiography, 3 sheaths (2 8F sheaths and 1 8.5Fr steerable sheath) were introduced into the left atrium. Then, using a circular mapping catheter (Lasso™, Biosense Webster Inc, Diamond Bar, CA, USA) placed on the ostium of each pulmonary vein (PV) atrium, encircling PV isolation was performed with a 3.5-mm tip, open-irrigated ablation catheter (Biosense Webster Inc) to achieve electric isolation of the PV potential. All ablation procedures were performed with a 3D electroanatomical mapping system (CARTO™, Biosense Webster Inc). The RF energy output was titrated to 25–35 W at a flow rate of 17–30 ml/min, with a maximum temperature of 42°C. For the most part, paroxysmal AF and early persistent AF required PV isolation alone, but in patients with prolonged persistent AF, atrial tachycardia, or evidence of non-PV foci, additional linear ablation and complex fractionated electrogram ablation were applied. If the patient did not convert to sinus rhythm at the end of the ablation procedure, internal cardioversion was performed. During the procedure, bolus and additional heparin were administered to maintain an activated clotting time of 300–350s.

Follow-up

Patients remained hospitalized under continuous rhythm monitoring for 3 days after the procedure. After discharge, patients were followed through the outpatient clinic at 1, 3, 6 months, and every 6 months after ablation. At one month after ablation, 24-hour Holter monitoring was performed in all patients. At the time of each follow-up visit, patients underwent 12-lead ECG, and were asked about any symptoms related to the presence of arrhythmia. If patients were suspected of having had an emerging arrhythmia, but had no evidence of the arrhythmia at the time of examination, additional Holter monitoring and short-duration follow-up were performed. Device interrogation was also used to detect any recurrence of AF or atrial tachycardia in patients with a history of device implantation. AF or atrial tachycardia occurring within 3 months (blanking period) after ablation was not considered to be a recurrence; however, repeat ablation during the blanking period was defined as AF recurrence. If the patient had an AF episode during the blanking period, antiarrhythmic drugs that had been discontinued before the procedure were re-administered. If no AF episode occurred beyond the blanking period after administration of antiarrhythmic drug therapy, successful ablation without recurrence was documented. Discontinuation of antiarrhythmic agents was decided on the basis of freedom from recurrence of any atrial arrhythmia for more than 3–6 months' follow-up after ablation. The primary follow-up endpoint of this study was the recurrence of any AF or atrial tachycardia of more than 30 s duration. Moreover, we defined major adverse events as all-cause death, HF hospitalization, and cerebral infarction after discharge of the catheter ablation procedure.

Laboratory Assessment and Other Testing

Blood samples were collected from a peripheral vein while the patient was supine after a rest period. The complete blood cell count and RDW were assessed using an XE-2100 automated hematology analyzer (Sysmex Inc, Kobe, Japan). The reference range for normal RDW values was 11.0–14.0%. The plasma B-type natriuretic peptide (BNP) concentration was measured with a specific immunoassay for human BNP (ARCHITECT BNP-JP kit, Abbott Japan Inc, Chiba, Japan). High-sensitivity C-reactive protein (hs-CRP) level was measured using human anti-CRP (CRP Ⅱ Latex X2, Denka Seiken, Tokyo, Japan). The blood tests, including RDW, were performed on admission the day prior to ablation.

The $CHADS_2$ and CHA_2DS_2-VASc scores were evaluated as previously described.[13,14] The eGFR was calculated on the basis of the Japanese coefficient-modified Modification of Diet in Renal disease study equation.[15] For the echocardiography parameters, LVEF was calculated using Simpson's method. The left atrial diameter (LAD), left ventricular end-diastolic and end-systolic diameters were assessed using M-mode methods. This retrospective study was performed in accordance with the Declaration of Helsinki. The patients' baseline characteristics, comorbidities, and therapeutic details were obtained from hospital medical records.

Statistical Analysis

Continuous variables are expressed as the mean±standard deviation or median (1st and 3rd quartiles), and categorical variables are expressed as number and percentage. Comparison of the differences in the baseline characteristics were performed using Student's t test for parametric data and Mann-Whitney U-tests for non-parametric data. Categorical variables were

Table 1. Comparison of the Demographic and Baseline Characteristics of the Non-HF and HF Groups

	Non-HF group (n=678)	HF group (n=79)	P value
Age, years	61.4±11.6	63.6±11.2	0.108
Male sex	512 (76%)	58 (73%)	0.682
BMI, kg/m²	24.3±6.9	23.6±3.7	0.386
Type of AF			
Paroxysmal	476 (70%)	30 (38%)	<0.001
Persistent	142 (21%)	37 (47%)	<0.001
Long-standing persistent	60 (9%)	12 (15%)	0.069
Duration of AF, years	2.0 (0.4–5.1)	0.8 (0.4–5.3)	0.198
Comorbidities			
Hypertension	308 (45%)	30 (38%)	0.207
Diabetes mellitus	86 (13%)	16 (20%)	0.062
Coronary artery disease	48 (7%)	8 (10%)	0.327
Stroke or TIA	56 (8%)	5 (6%)	0.551
Previous device implantation	16 (2%)	13 (17%)	<0.001
Laboratory data			
Hemoglobin, g/dl	14.0±1.5	13.7±2.1	0.073
WBC count (×10³/μl)	5.4±1.5	5.9±1.6	0.007
hs-CRP, mg/L	0.50 (0.30–1.10)	0.90 (0.40–2.02)	<0.001
RDW, %	13.2±0.8	14.0±1.6	<0.001
MCV, fl	92.1±4.3	91.8±5.6	0.476
Creatinine level, mg/dl	0.8±0.2	1.0±0.2	<0.001
eGFR, ml/min/1.73m²	74.5±20.6	61.3±17.1	<0.001
BNP level, pg/dl	40.7 (21.1–88.3)	148.8 (70.0–289.0)	<0.001
Total cholesterol, mg/dl	192.5±34.5	189.9±36.2	0.526
Albumin, g/dl	4.2±0.3	4.1±0.4	0.096
Echocardiographic data			
LAD, mm	38.5±6.3	42.9±7.7	<0.001
LVEDD, mm	48.9±5.0	53.4±9.1	<0.001
LVEDS, mm	32.3±4.6	40.7±10.8	<0.001
LVEF, %	62.1±6.7	46.4±15.1	<0.001
$CHADS_2$ score	0.9±1.0	1.9±1.0	<0.001
CHA_2DS_2-VASc score	1.6±1.5	2.8±1.5	<0.001
NYHA functional class	NA	2.1±0.7	NA
Medical therapy			
ACEI or ARB	236 (35%)	46 (58%)	<0.001
β-blockers	210 (31%)	66 (84%)	<0.001
Spironolactone	13 (2%)	49 (62%)	<0.001
Diuretic	23 (3%)	61 (77%)	<0.001
Digoxin	42 (6%)	17 (22%)	<0.001
Ablation procedure			
Pulmonary vein isolation	678 (100%)	79 (100%)	NA
Cavotricuspid isthmus	568 (84%)	70 (89%)	0.264
LA linear ablation	211 (31%)	43 (54%)	<0.001
CFAE	113 (17%)	28 (35%)	<0.001
Superior vena cava isolation	54 (8%)	9 (11%)	0.297

The data are presented as number (%), and mean±standard deviation or median (interquartile). Linear ablation includes roof, bottom, and mitral isthmus lines. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CFAE, complex fractionated electrogram; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LA, left atrial; LAD, LA diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEDS, left ventricular end-systolic diameter; MCV, mean corpuscular volume; NYHA, New York Heart Association; RDW, red blood cell distribution width; TIA, transient ischemic attack; WBC, white blood cell.

compared using the chi-square test or Fisher's exact test. The Kaplan-Meier method was used to estimate event-free survival, and the differences between the curves were compared using the log-rank test. The prognostic value of each factor was first evaluated by univariate Cox proportional hazard regression analysis. The factors that had P-values <0.05 in the univariate analysis were entered into a multivariate Cox proportional hazards model to identify the independent predictors.

Table 2. Comparison of the Demographic and Baseline Characteristics of the Non-Recurrence and Recurrence Groups of Non-HF and HF Patients

	Non-HF group (n=678)		P value	HF group (n=79)		P value
	Non-recurrence (n=409)	Recurrence (n=269)		Non-recurrence (n=37)	Recurrence (n=42)	
Age, years	61.6±12.0	61.1±11.1	0.523	63.0±10.6	64.2±11.8	0.647
Male sex	305 (75%)	202 (77%)	0.481	32 (87%)	26 (62%)	0.014
BMI, kg/m²	24.3±8.3	24.3±3.7	0.999	24.0±3.2	23.3±4.0	0.340
Type of AF						
Paroxysmal	295 (72%)	181 (67%)	0.178	10 (27%)	20 (48%)	0.060
Persistent	87 (21%)	55 (20%)	0.796	23 (62%)	14 (33%)	0.010
Long-standing persistent	27 (7%)	33 (12%)	0.011	4 (11%)	8 (19%)	0.309
Duration of AF, years	2.0 (0.4–5.0)	2.0 (0.4–6.0)	0.110	0.8 (0.4–2.6)	0.9 (0.4–7.3)	0.327
Comorbidities						
Hypertension	183 (45%)	125 (47%)	0.660	18 (47%)	12 (29%)	0.067
Diabetes mellitus	54 (13%)	32 (12%)	0.617	6 (16%)	10 (24%)	0.402
Coronary artery disease	30 (7%)	18 (7%)	0.749	2 (5%)	6 (14%)	0.271
Stroke or TIA	27 (7%)	29 (11%)	0.053	1 (3%)	4 (10%)	0.364
Previous device implantation	10 (2%)	6 (2%)	0.857	3 (8%)	10 (24%)	0.060
Laboratory data						
Hemoglobin, g/dl	14.0±1.5	14.0±1.5	0.741	14.1±1.8	13.3±2.3	0.092
WBC count (×10³/μl)	5.3±1.6	5.5±1.4	0.273	6.1±1.6	5.7±1.5	0.311
hs-CRP, mg/L	0.50 (0.20–1.10)	0.50 (0.30–1.10)	0.327	1.00 (0.40–2.20)	0.80 (0.40–2.00)	0.598
RDW, %	13.2±0.8	13.3±0.8	0.332	13.5±0.9	14.5±2.0	0.013
MCV, fl	92.0±4.2	92.3±4.4	0.407	92.3±4.6	91.3±6.4	0.432
Creatinine level, mg/dl	0.8±0.2	0.8±0.2	0.338	1.0±0.2	1.0±0.2	0.880
eGFR, ml/min/1.73 m²	74.4±16.0	74.5±26.1	0.950	62.8±16.2	60.0±18.0	0.481
BNP level, pg/dl	38.0 (19.4–83.8)	47.8 (23.7–93.2)	0.039	142.0 (59.2–264.2)	165.2 (87.4–329.6)	0.369
Total cholesterol, mg/dl	193.3±34.7	191.4±34.1	0.494	190.4±32.2	189.5±39.8	0.905
Albumin, g/dl	4.1±0.4	4.2±0.3	0.921	4.2±0.4	4.0±0.5	0.277
Echocardiographic data						
LAD, mm	38.1±6.2	39.2±6.4	0.018	40.9±7.3	44.7±7.8	0.032
LVEDD, mm	48.5±4.9	49.7±4.9	0.003	53.9±6.4	53.1±11.1	0.704
LVEDS, mm	31.8±4.5	32.9±4.6	0.001	40.7±8.0	40.7±12.9	0.970
LVEF, %	62.4±6.8	61.6±6.5	0.164	45.8±15.1	46.9±15.2	0.757
$CHADS_2$ score	0.9±1.0	0.9±1.1	0.501	1.8±0.8	1.9±1.3	0.707
CHA_2DS_2-VASc score	1.7±1.5	1.6±1.5	0.675	2.5±1.2	3.0±1.7	0.133
NYHA functional class	NA	NA	NA	2.2±0.7	1.9±0.7	0.097
Medical therapy						
ACEI or ARB	142 (35%)	92 (35%)	0.952	20 (54%)	26 (62%)	0.480
β-blockers	120 (29%)	90 (34%)	0.257	29 (78%)	37 (88%)	0.245
Spironolactone	8 (2%)	5 (2%)	0.928	25 (68%)	24 (57%)	0.341
Diuretic	15 (4%)	8 (3%)	0.626	28 (76%)	33 (79%)	0.759
Digoxin	23 (6%)	19 (7%)	0.447	10 (27%)	7 (17%)	0.264
Ablation procedure						
Pulmonary vein isolation	409 (100%)	269 (100%)	NA	37 (100%)	42 (100%)	NA
Cavotricuspid isthmus	343 (84%)	225 (84%)	0.939	31 (84%)	39 (93%)	0.292
LA linear ablation	130 (32%)	81 (30%)	0.672	23 (62%)	20 (48%)	0.195
CFAE	66 (16%)	47 (18%)	0.648	13 (35%)	15 (36%)	0.957
Superior vena cava isolation	25 (6%)	29 (11%)	0.028	7 (19%)	2 (5%)	0.075
Antiarrhythmic drug use at follow-up						
Class I	53 (13%)	97 (36%)	<0.001	1 (3%)	9 (21%)	0.012
Class III	14 (3%)	41 (15%)	<0.001	7 (19%)	10 (24%)	0.598
None	342 (84%)	131 (49%)	<0.001	29 (78%)	23 (55%)	0.027

Data are presented as number (%), and mean±standard deviation or median (interquartile). Abbreviations as in Table 1.

Table 3. Predictors of Baseline Characteristics for Recurrence of AF in Univariate and Multivariate Regression Analyses in the Non-HF and HF Groups

	Non-HF group				HF group			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, year	0.99 (0.99–1.01)	0.470			1.01 (0.98–1.03)	0.662		
Female	0.87 (0.66–1.16)	0.341			2.86 (1.51–5.45)	0.001*	2.43 (1.22–4.88)	0.012*
BMI, kg/m^2	1.00 (0.99–1.02)	0.814			0.93 (0.84–1.01)	0.098		
Non-PAF	1.21 (0.94–1.56)	0.149			0.62 (0.34–1.15)	0.131		
Duration of AF, years	1.02 (1.00–1.04)	0.046*	1.02 (0.99–1.04)	0.073	1.03 (0.97–1.09)	0.302		
Class III antiarrhythmic drug use at follow-up	2.67 (1.91–3.72)	0.001*	2.27 (1.59–3.24)	0.001*	1.40 (0.68–2.85)	0.363		
Hypertension	1.08 (0.85–1.38)	0.519			0.62 (0.32–1.20)	0.156		
Diabetes mellitus	0.98 (0.68–1.42)	0.924			1.51 (0.73–3.11)	0.264		
Coronary artery disease	0.90 (0.56–1.45)	0.666			1.12 (0.46–2.66)	0.816		
Stroke or TIA	1.57 (1.07–2.31)	0.022*	1.62 (1.10–2.39)	0.014*	2.36 (0.83–6.66)	0.106		
Hemoglobin, g/L	0.98 (0.90–1.05)	0.515			0.88 (0.75–1.03)	0.105		
WBC count, $10^3\mu$l	1.03 (0.96–1.11)	0.444			0.91 (0.74–1.12)	0.373		
hs-CRP, mg/L	0.92 (0.66–1.29)	0.630			1.22 (0.84–1.76)	0.290		
RDW, %	1.07 (0.93–1.23)	0.378			1.30 (1.12–1.52)	0.001*	1.20 (1.01–1.40)	0.034*
MCV, fl	1.01 (0.98–1.04)	0.465			0.96 (0.89–1.02)	0.196		
Creatinine level, mg/dl	1.52 (0.79–2.91)	0.209			1.31 (0.31–5.58)	0.713		
eGFR, ml/min/1.73 m^2	0.99 (0.99–1.01)	0.870			0.99 (0.97–1.01)	0.270		
BNP level, pg/dl	1.00 (1.00–1.01)	0.001*	1.00 (1.00–1.01)	0.010*	1.01 (1.00–1.01)	0.037*	1.00 (1.00–1.00)	0.442
Total cholesterol, mg/dl	1.00 (0.99–1.00)	0.063			1.00 (0.99–1.01)	0.925		
Albumin, g/dl	1.08 (0.77–1.53)	0.662			0.73 (0.37–1.40)	0.340		
LAD, mm	1.02 (1.00–1.04)	0.020*	0.99 (0.97–1.02)	0.591	1.03 (0.99–1.07)	0.136		
LVEDD, mm	1.03 (1.01–1.06)	0.009*	1.01 (0.97–1.06)	0.547	0.99 (0.95–1.03)	0.683		
LVEDS, mm	1.04 (1.02–1.07)	0.002*	1.02 (0.98–1.07)	0.310	1.01 (0.98–1.04)	0.728		
LVEF, %	0.99 (0.97–01)	0.209			1.00 (0.98–1.02)	0.881		

*P<0.05. CI, confidence interval; HR, hazard ratio; PAF, paroxysmal AF. Other abbreviations as in Table 1.

Based on the obtained significant predictors, a receiver-operating characteristic (ROC) curve was plotted, and the cut-off point for the ROC curve factor was determined. Bland-Altman difference plots with 95% confidence limits were constructed to evaluate the degree of agreement between the 2 measurements.[16] The 95% limits of agreement were calculated as the mean difference±2 standard deviations. P<0.05 was considered statistically significant.

Results

A total of 757 patients were included in the present study. Of them, 79 were in the HF group, and 678 were in the non-HF group. Baseline characteristics and examination results between the HF and non-HF groups are shown in Table 1. The HF patients had a lower prevalence of paroxysmal AF and higher prevalence of persistent AF and a history of device implantation. In the laboratory data, white blood cell count, hs-CRP levels, RDW, creatinine levels, eGFR, and plasma BNP levels

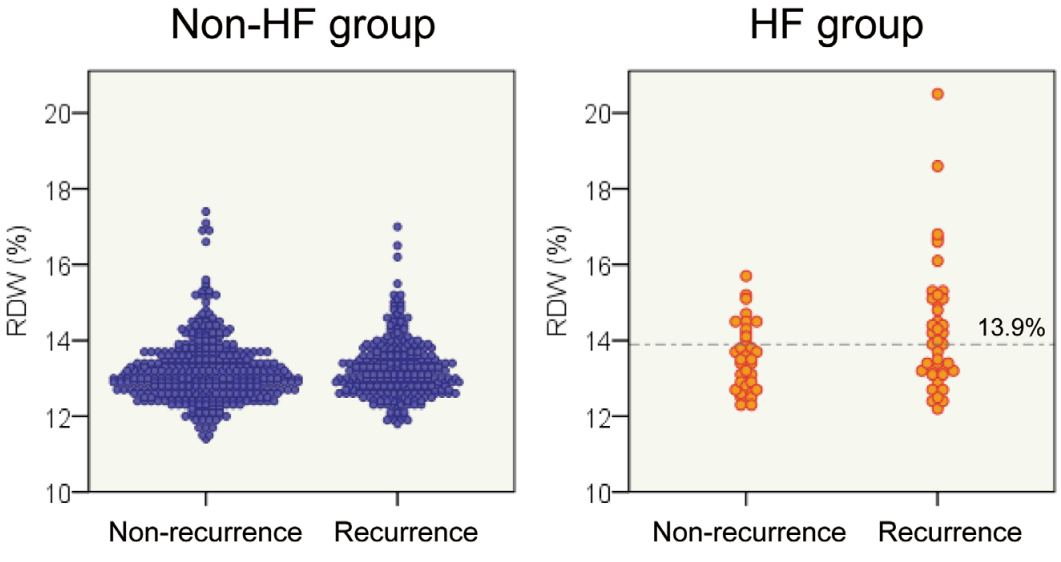

Figure 1. Red blood cell distribution width (RDW) distribution divided into recurrence and non-recurrence groups among patients with and without heart failure (HF).

were higher in the HF group than in the non-HF group. Significant differences were observed between the 2 groups in echocardiographic parameters, $CHADS_2$ and CHA_2DS_2-VASc scores, prevalence of medication therapies, and ablation procedures.

During a follow-up period (mean=22.3±16.7 months) after catheter ablation, recurrence of AF was observed in 311 patients (41%) in the total population. There was a significant difference in recurrence of AF between the HF and non-HF groups (42 patients [53%] vs. 269 patients [40%], P=0.021). Repeat CA was performed in 213 patients (HF group; 24 patients [30%] vs. non-HF group; 189 patients [28%], P=0.640) during the study period. During a repeat ablation procedure, a PV reconnection was found in 18 (75%) and 161 (85%) patients (P=0.234), and the mean number of PV reconnections was 2.1±1.0 and 2.4±1.0 (P=0.139) in the HF and non-HF groups, respectively. Class I and Class Ⅲ antiarrhythmic drugs were administered to 160 (133 during a blanking period) and 72 patients (66 during a blanking period) in the total population.

Within the HF group, a comparison of the baseline characteristics and examination data of the recurrence and non-recurrence groups is shown in **Table 2**. Female sex and reduced prevalence of persistent AF were more common in the recurrence group than in the non-recurrence group. The baseline RDW was greater in the recurrence group than in the non-recurrence group (14.5±2.0% vs. 13.5±0.9%, P=0.013). Moreover, a significant difference in LAD was observed. In contrast, for the non-HF group, prevalence of long-standing persistent AF and BNP levels were higher in the recurrence group than in the non-recurrence group. On echocardiography, LAD, and the LV end-diastolic and -systolic diameters were greater in the recurrence group. No significant difference in RDW at baseline was observed between the recurrence and non-recurrence groups (13.3±0.8% vs. 13.2±0.8%, P=0.332).

Univariate Cox proportional hazard regression analysis demonstrated that duration of AF, Class Ⅲ antiarrhythmic drug administration at follow-up, stroke, BNP level, LAD, and LV end-diastolic and -systolic diameters were significantly associated with recurrence in the non-HF group. In contrast, female sex, RDW, and BNP levels were significant factors in recurrence in the HF group. Multivariate analyses showed that Class Ⅲ antiarrhythmic drug use (hazard ratio [HR] 2.27, 95% confidence interval [CI] 1.59–3.24, P=0.001), stroke (HR 1.62, 95% CI 1.10–2.39, P=0.014), and BNP level (HR 1.00, 95% CI 1.00–1.01, P=0.010) were independent predictors of AF recurrence in the non-HF group, while female sex (HR 2.43, 95% CI 1.22–4.88, P=0.012) and RDW (HR 1.20, 95% CI 1.01–1.40, P=0.034) were independent predictors for AF recurrence in the HF group (**Table 3**).

In the HF group, the cut-off value of RDW for AF recurrence based on ROC curve was 13.9% (area under the curve 0.63, 95% CI 0.51–0.75) with a specificity of 70% and sensitivity of 55%. The prevalence of RDW ≥13.9% was significantly higher in the recurrence group than in the non-recurrence group (23 patients [68%] vs. 11 patients [32%], P=0.025). The distributions of RDW divided into recurrence and non-recurrence groups are shown in **Figure 1**. An overlap of RDW was found between the recurrence and non-recurrence groups in patients with HF; nevertheless, some cases of recurrence in the HF group had a high RDW value with variability. Moreover, major adverse events occurred in 12 patients (all-cause death in 3 and HF hospitalization in 11) in the HF group. The detailed cause of death was decompensated HF in 2 patients and sepsis in 1. A comparison of the demographic and baseline characteristics of patients in the HF group with and without major adverse events is shown in **Table 4**. Baseline RDW values were higher in patients with major adverse events than in patients without them (15.0±2.2% vs. 13.8±1.5%, P=0.025). Moreover, the post-ablation AF recurrence rate was higher in patients with major adverse events than in those without them (92% vs. 46%, P=0.004). Subsequent multivariate Cox proportional hazards analysis demonstrated that RDW was an independent predictor of major adverse events in the HF group (HR 1.83, 95% CI 1.13–2.72, P=0.003). The cut-off value of RDW for major adverse events in the HF group based on ROC curve

Table 4. Comparison of Demographic and Baseline Characteristics of Patients With and Without Major Adverse Events in the HF Group

	Non-major adverse events group (n=67)	Major adverse events group (n=12)	P value
Age, years	63.2±11.3	66.1±10.6	0.411
Male sex	50 (75%)	8 (67%)	0.723
BMI, kg/m²	23.9±3.6	22.0±3.9	0.088
Type of AF			
Paroxysmal	21 (31%)	9 (75%)	0.008
Persistent	36 (54%)	1 (8%)	0.004
Long-standing persistent	10 (15%)	2 (17%)	0.999
Duration of AF, years	0.9 (0.4–4.5)	0.8 (0.4–7.8)	0.945
Comorbidities			
Hypertension	26 (39%)	4 (33%)	0.999
Diabetes mellitus	12 (18%)	4 (33%)	0.249
Coronary artery disease	6 (9%)	2 (17%)	0.600
Stroke or TIA	3 (5%)	2 (17%)	0.163
Previous device implantation	9 (14%)	4 (33%)	0.103
Laboratory data			
Hemoglobin, g/dl	13.9±2.1	12.7±1.9	0.082
WBC count (×10³/μl)	5.9±1.6	5.7±1.0	0.718
hs-CRP, mg/L	0.4 (0.80–1.90)	1.6 (0.5–4.2)	0.221
RDW, %	13.8±1.5	15.0±2.2	0.025
MCV, fl	92.0±5.6	90.6±6.0	0.422
Creatinine level, mg/dl	1.0±0.2	1.0±0.3	0.376
eGFR, ml/min/1.73m²	62.3±17.2	55.7±16.3	0.218
BNP level, pg/dl	127.9 (55.7–252.8)	277.6 (165.5–719.3)	0.004
Total cholesterol, mg/dl	189.8±35.6	190.8±41.3	0.931
Albumin, g/dl	4.1±0.4	4.0±0.5	0.273
Echocardiographic data			
LAD, mm	42.5±8.1	45.3±4.6	0.242
LVEDD, mm	52.4±8.7	59.4±9.6	0.013
LVEDS, mm	39.2±10.2	48.9±11.3	0.004
LVEF, %	49.1±14.3	31.3±9.6	<0.001
$CHADS_2$ score	1.8±0.9	2.2±1.6	0.323
CHA_2DS_2-VASc score	2.6±1.4	3.4±2.0	0.103
NYHA functional class	2.0±0.6	2.5±1.1	0.022
Medical therapy			
ACE-Is or ARBs	38 (57%)	8 (67%)	0.520
β-blockers	54 (81%)	12 (100%)	0.199
Spironolactone	39 (58%)	10 (83%)	0.119
Diuretic	49 (73%)	12 (100%)	0.058
Digoxin	16 (24%)	1 (8%)	0.445
Ablation procedure			
Pulmonary vein isolation	67 (100%)	12 (100%)	NA
Cavotricuspid isthmus	60 (90%)	10 (83%)	0.620
LA linear ablation	36 (54%)	7 (58%)	0.768
CFAE	23 (34%)	5 (42%)	0.745
Superior vena cava isolation	9 (13%)	0 (0%)	0.341
Recurrence of AF after ablation	31 (46%)	11 (92%)	0.004

Data are presented as number (%), and mean±standard deviation or median (interquartile). Other abbreviations as in Table 1.

analysis was 14.8% (area under the curve 0.71, 95% CI 0.56–0.86) with a specificity of 85% and sensitivity of 56%. Kaplan-Meier curves demonstrated significant differences within the HF group both in event-free survival for recurrence of AF (RDW ≥13.9% and <13.9%, P=0.019) and for major adverse events (RDW ≥14.8% and <14.8%, P<0.001) (Figure 2).

We divided the non-HF group into 3 groups according to 1st and 3rd quartiles of RDW, and compared the outcomes among them (RDW ≥13.6%; n=181, 13.6%>RDW≥12.7%; n=340, and RDW <12.7%; n=157). With regards to the recurrence of AF after ablation, there was no difference in event-free survival among the 3 groups (P=0.585) (Figure 3A). In

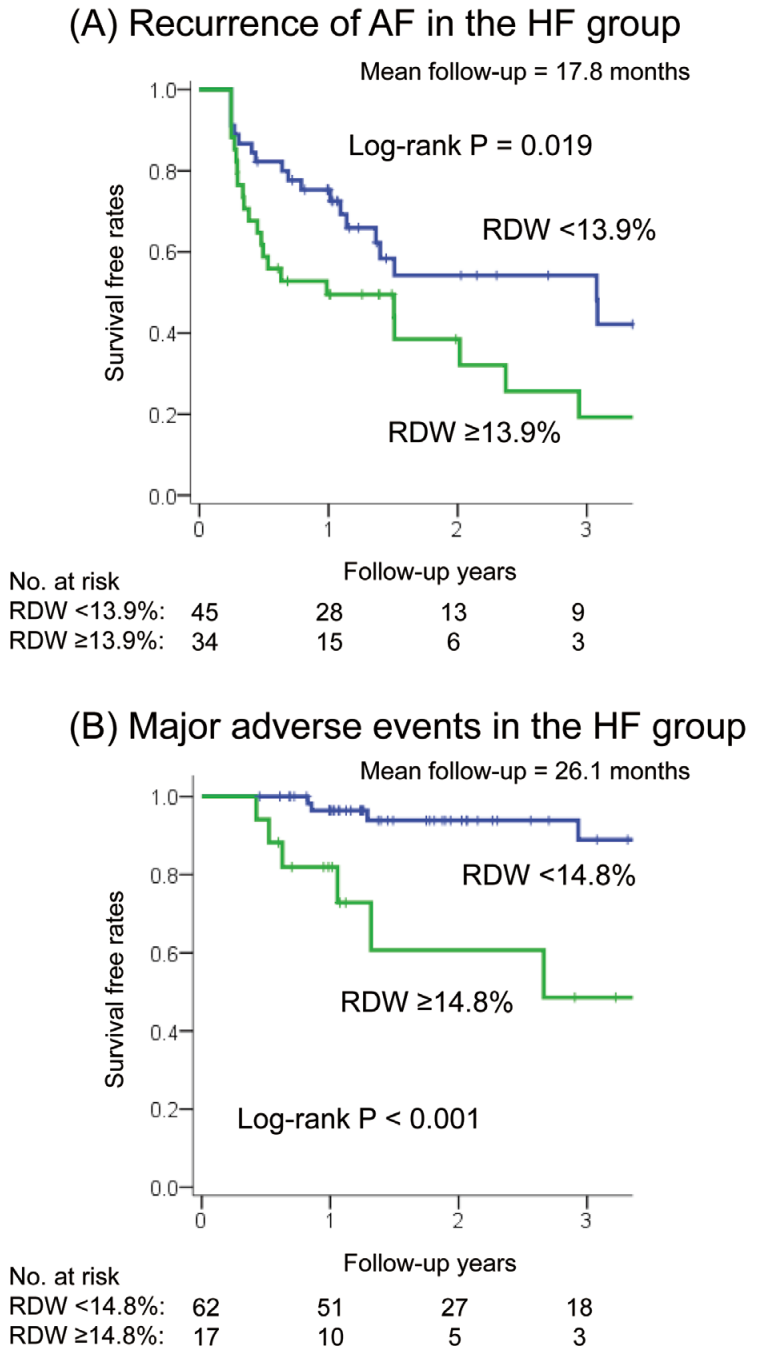

Figure 2. Comparison of the Kaplan-Meier survival curves of the recurrence of atrial fibrillation (AF) (**A**) and major adverse events (**B**) after catheter ablation in patients with heart failure (HF) among the 2 groups according to each cut-off RDW value (recurrence of AF: RDW 13.9% and major adverse events: RDW 14.8%). RDW, red blood cell distribution width.

addition, major adverse events occurred in 5 patients (2 HF hospitalizations, 2 strokes, and 1 death from cancer) among the non-HF patients. Anticoagulant drug therapy was continued at the time of stroke in 1 patient but not in the other because of post-ablation AF non-recurrence. Kaplan-Meier curves demonstrated no significant difference regarding major adverse events among the 3 groups (P=0.874) (**Figure 3B**).

Furthermore, the patients in the HF group were divided into impaired LVEF (LVEF ≤40%, n=30) and preserved LVEF (LVEF >40%, n=49) groups. A comparison of the baseline characteristics of the 2 groups is shown in **Table 5**. Baseline RDW did not differ significantly between the impaired and preserved LVEF groups (14.2±1.7% and 13.9±1.6%, P=0.593). The post-ablation AF recurrence rates were comparable in the 2 groups (50% vs. 55%, P=0.659, respectively). In the preserved LVEF group, multivariate Cox proportional hazards analysis revealed that high RDW exhibited a trend toward an association with AF recurrence after ablation (HR 1.23, 95% CI 0.97–1.54, P=0.082), while the predictive value of RDW was not significant in the impaired LVEF group (HR 0.93, 95% CI 0.61–1.43, P=0.740) (**Table S1**).

We also assessed the RDW value 3 weeks prior to the CA procedure in the outpatient clinic, and the mean RDW values were 13.2±0.8% and 13.9±1.7% in the non-HF (606 patients)

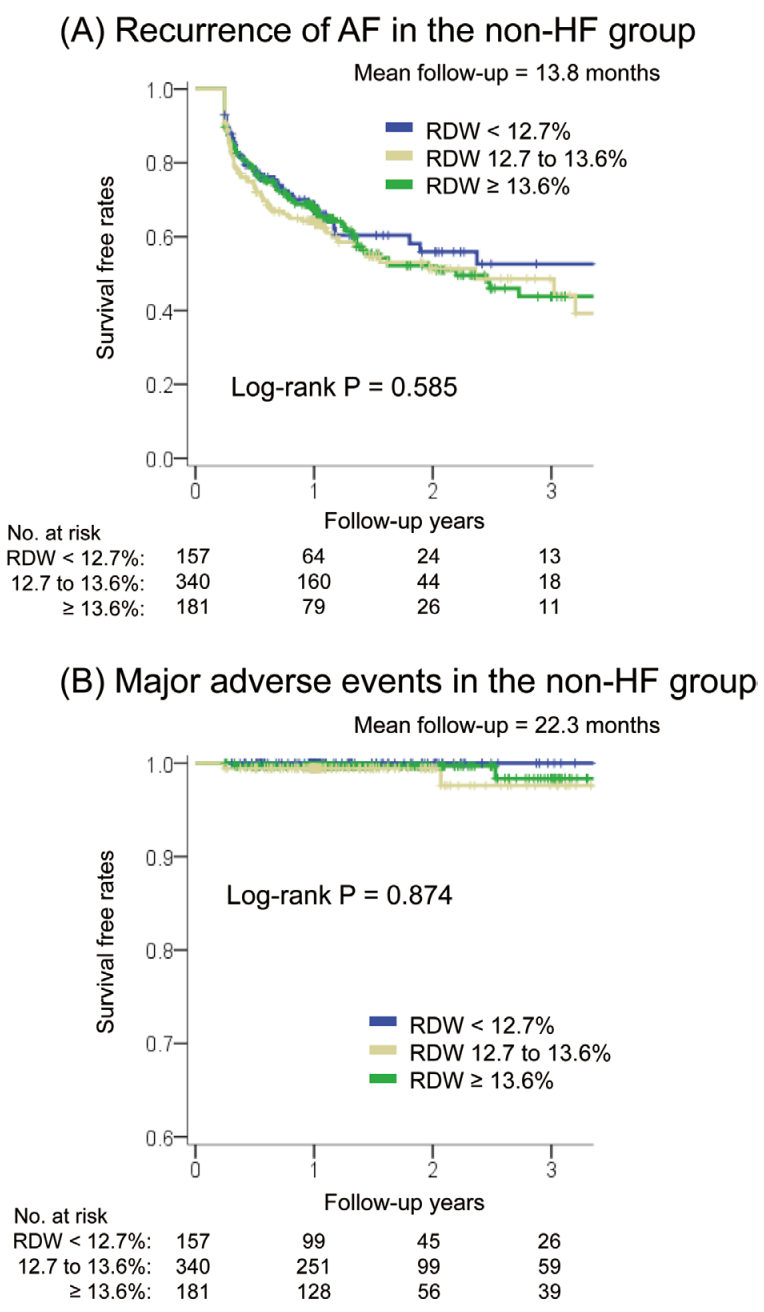

Figure 3. Comparison of the Kaplan-Meier survival curves of the recurrence of atrial fibrillation (AF) (**A**) and major adverse events (**B**) after catheter ablation in patients with non-heart failure among the 3 groups (RDW ≥13.6%; n=181, 13.6%>RDW≥12.7%; n=340, and RDW <12.7%; n=157). HF, heart failure; RDW, red blood cell distribution width.

and HF (79 patients) groups, respectively. To evaluate the agreement between the RDW values at baseline and 3 weeks before ablation, a Bland-Altman analysis was performed, and the results indicated that the mean differences with 95% limits of agreement were −0.007% (−0.535 to 0.521) and 0.098% (−1.221 to 1.416) in the non-HF and HF groups, respectively (**Figure S1**). The slopes of the regression line in the Bland-Altman plot indicated no proportional bias in the non-HF (r=0.022, P=0.582) and HF groups (r=−0.062, P=0.585).

Discussion

The present study demonstrated an association between RDW and prognosis after RFCA in patients with AF. High RDW had a significant relationship with recurrence of AF after CA for AF in HF patients, but not in non-HF patients. Furthermore, high RDW predicted major adverse events after CA of AF among the HF patients.

Recent studies have shown a relationship between RDW and mortality among patients with cardiovascular diseases.[2–6] Although higher RDW was associated with AF incidence in a population-based cohort and in postoperative patients,[7,8] there are limited data regarding the relationship between RDW and prognosis in patients undergoing CA of AF. Gurses et al recently reported that elevated RDW was found to be a significant predictor of late recurrence in 299 patients scheduled for cryoballoon-based AF ablation.[9] Another study showed an association between high RDW and AF recurrence after cryoballoon abla-

Table 5. Comparison of Demographic and Baseline Characteristics of the Preserved LVEF (LVEF >40%) and Impaired LVEF (LVEF ≤40%) Groups of Patients With HF

	LVEF >40% (n=49)	LVEF ≤40% (n=30)	P value
Age, years	64.8±10.6	61.8±12.1	0.252
Male sex	34 (69%)	24 (80%)	0.300
BMI, kg/m²	24.4±3.6	22.9±3.6	0.189
Type of AF			
Paroxysmal	19 (39%)	11 (37%)	0.851
Persistent	24 (49%)	13 (43%)	0.625
Long-standing persistent	6 (12%)	6 (20%)	0.351
Duration of AF, years	0.8 (0.4–4.5)	0.8 (0.5–8.7)	0.354
Comorbidities			
Hypertension	20 (41%)	10 (33%)	0.506
Diabetes mellitus	11 (22%)	5 (17%)	0.535
Coronary artery disease	4 (8%)	4 (13%)	0.470
Stroke or TIA	2 (4%)	3 (10%)	0.362
Previous device implantation	6 (12%)	7 (23%)	0.223
Laboratory data			
Hemoglobin, g/dl	13.5±1.8	14.1±2.5	0.223
WBC count (×10³ μl)	6.0±1.6	5.7±1.5	0.389
hs-CRP, mg/L	0.80 (0.40–1.65)	1.00 (0.55–3.18)	0.129
RDW, %	13.9±1.6	14.2±1.7	0.593
MCV, fl	91.3±4.4	92.5±7.2	0.392
Creatinine level, mg/dl	0.9±0.2	1.0±0.3	0.030
eGFR, ml/min/1.73m²	62.7±16.3	59.0±18.4	0.348
BNP level, pg/dl	115.0 (47.4–208.2)	225.7 (118.5–490.3)	0.003
Total cholesterol, mg/dl	186.5±33.2	195.5±40.7	0.283
Albumin, g/dl	4.1±0.4	4.1±0.5	0.880
Echocardiographic data			
LAD, mm	42.2±7.5	44.1±8.1	0.279
LVEDD, mm	49.6±6.9	59.7±8.9	<0.001
LVEDS, mm	34.8±6.7	50.4±9.2	<0.001
LVEF, %	56.2±8.3	30.3±8.2	<0.001
$CHADS_2$ score	1.9±1.1	1.8±1.1	0.732
CHA_2DS_2-VASc score	2.8±1.5	2.6±1.5	0.565
NYHA functional class	2.0±0.6	2.2±0.8	0.102
Medical therapy			
ACEI or ARB	30 (61%)	16 (53%)	0.490
β-blockers	40 (82%)	26 (87%)	0.756
Spironolactone	28 (57%)	21 (70%)	0.253
Diuretic	36 (74%)	24 (83%)	0.310
Digoxin	10 (20%)	7 (23%)	0.759
Ablation procedure			
Pulmonary vein isolation	49 (100%)	30 (100%)	NA
Cavotricuspid isthmus	42 (86%)	28 (93%)	0.470
LA linear ablation	23 (47%)	20 (67%)	0.088
CFAE	16 (33%)	12 (40%)	0.508
Superior vena cava isolation	5 (10%)	4 (13%)	0.724

Data are presented as number (%), and mean±standard deviation or median (interquartile). Abbreviations as in Table 1.

tion in 49 patients.[10] However, data from a large sample for assessing pre-ablation RDW and prognosis after CA of AF do not yet exist. In our assessment of 757 patients with AF divided into HF and non-HF groups, we found a significant relationship between RDW and recurrence of AF after RFCA in HF patients but not in non-HF patients. Our findings provide an additional viewpoint regarding the recurrence of AF after CA for AF patients complicated with HF.

Although the mechanisms underlying the association between higher RDW and poor prognosis are not clearly determined, several possible explanations can be considered in HF patients. Increased activation of the renin-angiotensin system and adrenergic hormones in HF could cause increased RDW with erythropoiesis and reduced cardiac function, resulting in poor

prognosis.[17] The changes in erythrocyte volume seem to affect the carriage of oxygen to tissues and are associated with free radical and oxidative stress.[7,18] This stress also reduces red blood cell survival and could influence RDW. Moreover, inflammation may have an important role in the regulation of RDW by inhibiting the activity of erythropoietin.[4,19–21] Several pro-inflammatory cytokines, which are linked to HF, may affect erythropoietin-induced erythrocyte maturation, and decreased erythrocyte maturation could cause a high RDW. Activated inflammatory state has been reported as an important factor in the incidence and maintenance of AF.[22] Thus, a possible association between AF and elevated RDW may be considered. All of the abovementioned speculations were based on HF states, and it is plausible that RDW was a prognostic factor in HF patients but not in non-HF patients in the present study. However, inflammatory markers such as hs-CRP and white blood cell count were not significantly associated with AF recurrence in either the HF or non-HF group in our results. The amount of direct inflammatory association between elevated RDW and recurrence of AF after ablation might be weaker than the influence of RDW in HF and other cardiovascular diseases themselves. Moreover, the baseline RDW values in the HF group were widely distributed compared with those in the non-HF group in our study, suggesting that RDW is sufficient to assess prognosis for patients involving 2 cardiovascular pathologies, AF and HF states after CA.

The predictive value of RDW for the recurrence of AF was observed strongly in patients with preserved LVEF compared with those with impaired LVEF. AF is a major etiology in the development of HF with preserved LVEF. It has been hypothesized that some part of the elevated RDW levels at baseline may be influenced by the AF burden in these patients, which could represent the possible association with AF recurrence during the follow-up period. We also found that most of the major adverse events were HF-related, and 92% of the patients with major adverse events had post-ablation AF recurrence, suggesting that RDW is a reasonable prognostic marker in patients with HF and AF. However, for the non-HF group, our finding of an insignificant correlation between RDW and prognosis is contrary to that of a previous study that reported a significant association between elevated RDW and AF recurrence among patients who underwent cryoballoon-based AF ablation.[9] The lower prevalence of male patients and persistent AF, lack of excluding HF patients with preserved LVEF (LVEF ≥50%), and small sample size in the former study were considered attributable to the contrasting results. Further large-sample prospective study with adequate power to evaluate RDW as a prognostic marker among non-HF AF patients after catheter ablation is required.

The clinical implication of the present study is that RDW is a potential noninvasive marker for HF patients with an increased recurrence rate following AF ablation. It could also be suggested that high RDW might be useful to guide monitoring (frequency of Holter monitoring or close follow-up) and clinical care (continuation of anticoagulation and antiarrhythmic medications) after CA.

Female sex was another independent predictor of post-ablation AF recurrence in the HF group. The lower efficacy of CA of AF in women and higher incidence of procedural complications than in men have been reported; the female patients with AF had more numerous non-PV foci, meaning that AF was less likely to be completely eliminated; additionally, they had a longer underlying history of AF prior to ablation than the male patients with AF.[23,24] Furthermore, women are also reportedly less likely to receive cardioprotective medications such as β-blockers compared with men with chronic HF.[25] These factors may have contributed to the poor outcomes of female patients with HF who underwent CA of AF in the present study.

Surprisingly, the traditional prognostic factors of LAD in both the HF and non-HF groups and plasma BNP level in the HF group were not found to be independent predictors for recurrence of AF after ablation therapy in the present study. Simple LAD measurement assessed using 2D M-mode methods sometimes fails to accurately present the whole LA volume.[26] Although a substantial rationale for the lack of a predictive LAD value is unclear, the LAD value was not a strong predictor of recurrence, which was overcome by other significant predictors on statistical analyses in this specific study population. Moreover, BNP levels at baseline were relatively widely distributed in the HF patients, so temporal BNP levels may be less likely to predict the recurrence of AF after CA than in lone AF patients.[27] It was also unusual that patients with persistent AF rather than paroxysmal AF in the HF group were likely to have fewer episodes of AF recurrence after ablation in the present study. We speculate that, in the HF group, patients with persistent AF were highly considered for selection for CA than those with paroxysmal AF because of the HF condition, and that the more curable persistent AF in HF patients would be subject to ablation therapy. The relatively shorter duration of AF in the HF group than in the non-HF group in this study cohort could support this speculation. Our results from the HF patients were drawn from a small-sample study, which is a potential limitation to evaluating prognosis including well-known prognostic factors.

Study Limitations

This was a retrospective study conducted at a single center. Although we used various monitoring tests to detect the recurrence of AF, asymptomatic short-duration AF may not have been detected in some cases, which could cause underestimation of the recurrence rate during the follow-up period.[28] Second, we excluded as much as possible patients with comorbidities likely to be associated with RDW. However, changes of RDW by some unknown underlying disease, or subclinical iron deficiency anemia from anticoagulant drug use, and concealed supplement intakes, which were not found through medical record review, were not completely excluded. Moreover, although differences in RDW between the 3 weeks before ablation and baseline were not significant in the HF and non-HF groups, a concern about RDW stability and variability, especially in patients with HF, which were measured at the specific time point, could exist. Third, stopping amiodarone 1 week before ablation was not enough to remove its effect on atrial electrophysiological properties. Finally, the mean LVEF and New York Heart Association functional class in HF patients indicated that the majority of the patients in the present study had relatively preserved LV function with mild to moderate HF.

Conclusions

In conclusion, high RDW was an independent prognostic marker for the recurrence of AF and major adverse events in patients with HF who underwent RFCA of AF. In contrast, RDW was not associated with recurrence of AF after CA in non-HF patients. In addition to the established factors for recurrence of AF after ablation, RDW is another prognostic marker in AF patients complicated with HF.

Disclosures

No conflict of interest.

References

1. Demir A, Yarali N, Fisgin T, Duru F, Kara A. Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. *Pediatr Int* 2002; **44:** 612–616.
2. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, et al; CHARM Investigators. Red cell distribution width as a novel prognostic marker in heart failure: Data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol* 2007; **50:** 40–47.
3. Pascual-Figal DA, Bonaque JC, Redondo B, Caro C, Manzano-Fernandez S, Sánchez-Mas J, et al. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. *Eur J Heart Fail* 2009; **11:** 840–846.
4. Forhecz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohaszka Z, Janoskuti L. Red cell distribution width in heart failure: Prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J* 2009; **158:** 659–666.
5. Borné Y, Smith JG, Melander O, Hedblad B, Engström G. Red cell distribution width and risk for first hospitalization due to heart failure: A population-based cohort study. *Eur J Heart Fail* 2011; **13:** 1355–1361.
6. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation* 2008; **117:** 163–168.
7. Adamsson Eryd S, Borné Y, Melander O, Persson M, Smith JG, Hedblad B, et al. Red blood cell distribution width is associated with incidence of atrial fibrillation. *J Intern Med* 2014; **275:** 84–92.
8. Ertaş G, Aydin C, Sönmez O, Erdoğan E, Turfan M, Tasal A, et al. Red cell distribution width predicts new-onset atrial fibrillation after coronary artery bypass grafting. *Scand Cardiovasc J* 2013; **47:** 132–135.
9. Gurses KM, Yalcin MU, Kocyigit D, Evranos B, Ates AH, Yorgun H, et al. Red blood cell distribution width predicts outcome of cryoballoon-based atrial fibrillation ablation. *J Interv Card Electrophysiol* 2015; **42:** 51–58.
10. Aksu T, Baysal E, Guler TE, Golcuk SE, Erden İ, Ozcan KS. Predictors of atrial fibrillation recurrence after cryoballoon ablation. *J Blood Med* 2015; **6:** 211–217.
11. JCS Joint Working Group. Guidelines for non-pharmacotherapy of cardiac arrhythmias (JCS 2011): Digest version. *Circ J* 2013; **77:** 249–274.
12. Nagao T, Inden Y, Yanagisawa S, Kato H, Ishikawa S, Okumura S, et al. Differences in the activated clotting time among uninterrupted anticoagulants during the periprocedural period of atrial fibrillation ablation. *Heart Rhythm* 2015; **12:** 1972–1978.
13. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285:** 2864–2870.
14. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. *Chest* 2010; **137:** 263–272.
15. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1:** 307–310.
17. Park TS, Zambidis ET. A role for the renin-angiotensin system in hematopoiesis. *Haematologica* 2009; **94:** 745–747.
18. Semba RD, Patel KV, Ferrucci L, Sun K, Roy CN, Guralnik JM, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: The Women's Health and Aging Study I. *Clin Nutr* 2010; **29:** 600–604.
19. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009; **133:** 628–632.
20. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *J Card Fail* 2010; **16:** 230–238.
21. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352:** 1011–1023.
22. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012; **60:** 2263–2270.
23. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm* 2010; **7:** 167–172.
24. Miyazaki S, Taniguchi H, Nakamura H, Takagi T, Iwasawa J, Hachiya H, et al. Clinical significance of early recurrence after pulmonary vein antrum isolation in paroxysmal atrial fibrillation: Insight into the mechanism. *Circ J* 2015; **79:** 2353–2359.
25. Sakata Y, Miyata S, Nochioka K, Miura M, Takada T, Tadaki S, et al. Gender differences in clinical characteristics, treatment and long-term outcome in patients with stage C/D heart failure in Japan: Report from the CHART-2 study. *Circ J* 2014; **78:** 428–435.
26. Kohári M, Zado E, Marchlinski FE, Callans DJ, Han Y. Left atrial volume best predicts recurrence after catheter ablation in patients with persistent and longstanding persistent atrial fibrillation. *Pacing Clin Electrophysiol* 2014; **37:** 422–429.
27. Hussein AA, Saliba WI, Martin DO, Shadman M, Kanj M, Bhargava M, et al. Plasma B-type natriuretic peptide levels and recurrent arrhythmia after successful ablation of lone atrial fibrillation. *Circulation* 2011; **123:** 2077–2082.
28. Senatore G, Stabile G, Bertaglia E, Donnici G, De Simone A, Zoppo F, et al. Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2005; **45:** 873–876.

Supplementary Files

Supplementary File 1

Table S1. Predictors of baseline characteristics for AF recurrence on univariate and multivariate regression analyses in the LVEF >40% and LVEF ≤40% groups among the HF patients

Figure S1. Bland-Altman plots of difference in RDW between baseline and 3 weeks before ablation against the mean of the 2 measurements in the non-HF group (**A**), and HF group (**B**).

Please find supplementary file(s);
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