Relationship between red blood cell distribution width levels and atrial fibrillation in hypertensive patients

Li-Hui ZHENG*, Shang-Yu LIU*, Feng HU, Zhi-Cheng HU, Li-Shui SHEN, Ling-Min WU, Yan YAO#
Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Abstract

Background Information on the relationship between red blood cell distribution width (RDW) and atrial fibrillation (AF) in patients with essential hypertension are scarce. The study aimed to assess the relationship between AF and RDW in hypertensive patients.

Methods We enrolled 432 hypertensive patients, including 350 AF patients and 82 patients as controls. Patients’ demographic, clinical, laboratory and echocardiographic characteristics were recorded. The AF patients were further divided into the persistent and paroxysmal AF subgroups. Electrocardiograms were monitored to identify the cardiac rhythm during blood sampling, and based on the rhythm, the paroxysmal AF group was categorized into the presence (with AF rhythm during blood sampling) and absence (with sinus rhythm during blood sampling) groups.

Results The AF group had elevated RDW levels than the controls (12.7% ± 0.8% vs. 12.4% ± 0.7%, P = 0.002), and the persistent AF subgroup had higher RDW levels than the paroxysmal AF subgroup (12.9% ± 0.8% vs. 12.6% ± 0.8%, P = 0.007). Furthermore, in the paroxysmal AF group, the presence group had higher RDW levels than the absence group (13.0% ± 0.6% vs. 12.5% ± 0.9%, P = 0.001).

Conclusions The RDW may be associated with the presence of AF rhythm, which implies the importance of maintaining the sinus rhythm in hypertensive patients.

J Geriatr Cardiol 2020; 17: 486–494. doi:10.11909/j.issn.1671-5411.2020.08.006

Keywords: Atrial fibrillation; Hypertension; Inflammation; Red blood cell distribution width

1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with considerable morbidity and mortality.[1,2] Hypertension is very common in AF patients. Evidence points towards a significant contribution of high blood pressure to AF incidence. In the Framingham Heart Study, hypertension and diabetes were demonstrated as the independent predictors for AF, and hypertension induced a 1.7-fold higher risk of AF in the population-based estimates.[3] Recent studies have demonstrated that inflammation plays a crucial role in the pathophysiology of AF.[4–7] Inflammation has also been implicated to be associated with hypertension.[8,9]

Red blood cell distribution width (RDW) is a measurement of the variability in the size of circulating erythrocytes and is obtained routinely in standard complete blood cell counts. The RDW has emerged as an independent and strong marker of adverse outcomes in patients with various cardiovascular disease states.[10–14] Increased RDW has been clearly associated with activated inflammatory state and oxidative stress in several pathological conditions.[15,16] Data on the relationship between RDW and AF in patients with essential hypertension are very limited.[17] This study aimed to investigate this association in hypertensive patients without significant comorbidities and associated cardiovascular conditions that may affect the RDW levels.

2 Methods

2.1 Study population

This case-control study enrolled consecutive patients who were admitted to our department from August 2015 to
September 2019. All hypertensive patients with AF were included, and hypertensive patients with paroxysmal supraventricular tachycardia (PSVT) were randomly enrolled in this study as controls.

No subjects had any heart abnormalities other than AF or PSVT. Hypertension was diagnosed as a systolic pressure of > 140 mmHg and/or a diastolic pressure > 90 mmHg or if the individual was taking antihypertensive medications. Paroxysmal AF was defined as having paroxysms of AF that terminated within 30 days of onset. Persistent AF was defined as AF lasting for > 30 days.[18]

The exclusion criteria were as follows: coronary artery disease, valvular heart disease, congenital heart disease, cardiomyopathy, left ventricular systolic dysfunction, previous cardiac surgery, hepatic or renal dysfunction, acute or chronic pulmonary embolism, chronic obstructive pulmonary disease, thyroid dysfunction, and established diagnosis of diabetes mellitus or sleep apnea. In addition, none of the participants had any history of inflammatory or infectious disease or recent (within the last four weeks) trauma or surgery; none was receiving treatment with nonsteroidal anti-inflammatory or corticosteroids drugs.

To explore the relationship between inflammation and AF, all the participants were divided into the AF and control groups. The AF group was further divided into the following two subgroups: paroxysmal and persistent AF subgroups. Moreover, the paroxysmal AF subgroup was further categorized into the presence (AF was present at the time of blood sampling) and absence (sinus rhythm was present at the time of blood sampling) groups.

All AF patients discontinued treatment of all anti-arrhythmic drugs at least for five half-lives prior to the enrollment in the study. Informed written consent was obtained from all patients, and this study was approved by the Ethics Committee of Fuwai Hospital (No.2015-ZX51) and clinical investigations are conducted according to the principles stipulated in the Declaration of Helsinki.

2.2 Study protocol

The flowchart of the study protocol and study groups has been shown in Figure 1. All participants provided a detailed medical history and underwent physical examinations, and laboratory and transthoracic echocardiographic examinations were performed.

The body mass index (BMI) was calculated as body weight (kg) divided by the square of the height (m) at the time of the admission. The thyroid function test, exercise stress test, nuclear cardiac imaging, and coronary CT angiography were performed. Echocardiography was performed to evaluate the left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), interventricular septal thickness

---

**Figure 1. The flowchart of the study and study subgroups.** IVST: interventricular septum thickness; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVPWT: left ventricular posterior wall thickness; RDW: red cell distribution width.
(IVST) and left ventricular posterior wall thickness (LVPWT).

Fasting venous blood samples were collected from the antecubital vein of the participants from 5:00 a.m. to 6:00 a.m. on the morning or on the second day of admission. All patients were monitored by electrocardiography at the time of blood sampling. The sinus rhythm was shown in all controls at the time of sampling. Blood samples were collected in tubes containing EDTA-treated or plain tubes. The complete blood count, including the total white blood cell (WBC) count, hemoglobin levels and RDW levels, was measured using an automated hematological analyzer (ST-1800i, Sysmex Corporation, Japan). The reference range for RDW level was 11.0%–11.5%. The inter-run coefficient of variation of the RDW assay during the study period was routinely < 1%.

2.3 Statistical analysis

Continuous data are reported as mean ± SD and categorical variables as percentage. The Kolmogorov-Smirnov statistic was used to test for normality of the distribution, and the variables with non-normally distributed scores were presented as median and interquartile range. With the continuous variables, group mean values were compared using the Student’s t-test and the Mann-Whitney U test if otherwise. Categorical variables were compared using the Pearson’s chi-square test.

Univariate and multivariate linear correlation test was used to analyze the relationship between the plasma RDW level and continuous variables. The covariates entered into the analyze model were age, gender, duration of hypertension, AF rhythm, BMI, smoking, aspirin, anticoagulation drugs, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), beta-blocker, diuretics, calcium channel blockers, statins, office systolic blood pressure, fasting blood glucose, potassium level and smoking history. There were also no significant differences between AF group and the controls in the ACEIs/ARBs, beta-blockers, diuretics, statins and calcium channels blockers used. Compared to the control group, the AF group was older and had increased LAD, IVST and LVPWT, respectively (Table 1).

Among the paroxysmal AF subgroup, the presence group had a larger LAD and higher level of office heart rate than the absence group, and there were no significant differences in the other indexes between the two groups.

The clinical and echocardiographic characteristics of the study populations are presented in Table 1.

3.2 RDW levels

3.2.1 AF groups compared to the control group

The RDW levels were significantly higher in the AF group than in the control group (12.7% ± 0.8% vs. 12.4% ± 0.7%, P = 0.002). Both the WBC count and hemoglobin level were also higher in the AF group than those of in the control group.

3.2.2 Paroxysmal and persistent AF subgroups compared to the control group

The persistent AF subgroup had a higher RDW level than the paroxysmal AF subgroup (12.9% ± 0.8% vs. 12.6% ± 0.8%, P = 0.007) and control group (12.9% ± 0.8% vs. 12.4% ± 0.7%, P = 0.001). The RDW level is higher in the paroxysmal AF subgroup than that in the control group (12.6% ± 0.8% vs. 12.4% ± 0.7%, P = 0.018). The WBC count was higher in the paroxysmal AF subgroup and persistent AF subgroup, compared to control group (P > 0.05) (Table 1).

3.2.3 Persistent AF group, presence and absence groups of the paroxysmal AF subgroup, and control group

The persistent AF subgroup had an elevated RDW level, which is similar to that of the presence group of the paroxysmal AF subgroup (12.9% ± 0.8% vs. 13.0% ± 0.6%, P = 0.07). Moreover, there was no significant difference in the RDW level between the absence group of the paroxysmal AF subgroup and control group (12.5% ± 0.9% vs. 12.4% ± 0.7%, P = 0.262) (Figure 2).
Table 1. Baseline characteristics of study populations.

| Characteristic            | Control group  | AF (n = 350) | P-value* | Persistent AF (n = 77) | P-value* | Paroxysmal AF (n = 273) | P-value* |
|---------------------------|----------------|-------------|----------|------------------------|----------|-------------------------|----------|
| Age, yrs                  |                |             |          |                        |          |                         |          |
| Male                      | 55 (67.1%)     | 240 (68.6%) | 0.793    | 63 (81.8%)             | 0.034    | 177 (64.8%)             | 0.709    |
| Smoking                   |                |             |          |                        |          |                         |          |
| Duration of hypertension, yrs | 6 (4–9)³     | 8 (6–11)³   | 0.001    | 8 (6–12)³              | 0.001    | 8 (6–11)³               | 0.001    |
| BMI, kg/m²                | 24.2 ± 2.6     | 24.7 ± 2.4  | 0.167    | 25.2 ± 2.6             | 0.023    | 24.5 ± 2.3              | 0.422    |
| Office heart rate, beats/min | 5.4 ± 1.3     | 5.7 ± 1.8   | 0.001    | 6.2 ± 2.0              | 0.002    | 5.5 ± 1.7               | 0.001    |
| Office SBP, mmHg          | 146.1 ± 10.4   | 145.1 ± 5.8 | 0.018    | 146.5 ± 5.2            | 0.018    | 144.7 ± 5.9             | 0.110    |
| Office DBP, mmHg          | 88.5 ± 10.2    | 90.2 ± 9.5  | 0.152    | 92.0 ± 8.1             | 0.019    | 89.7 ± 9.9              | 0.338    |
| WBC, ×10⁹/L              | 139.8 ± 16.2   | 143.5 ± 16.3| 0.063    | 149.7 ± 15.4           | 0.001    | 141.7 ± 16.2            | 0.334    |
| Hb, g/L                   | 12.4 ± 0.7     | 12.7 ± 0.8  | 0.002    | 12.9 ± 0.8             | 0.001    | 12.6 ± 0.8              | 0.018    |
| Creatinine, µmol/L        | 77.5 ± 12.4    | 80.6 ± 16.7 | 0.108    | 86.5 ± 18.0            | 0.001    | 79.0 ± 16.0             | 0.436    |
| TG, mmol/L                | 4.8 ± 0.4      | 4.9 ± 0.5   | 0.076    | 5.0 ± 0.4              | 0.023    | 4.9 ± 0.5               | 0.141    |
| HDL-c, mmol/L            | 1.4 ± 0.1      | 1.4 ± 0.2   | 0.018    | 1.3 ± 0.1              | 0.696    | 1.4 ± 0.2               | 0.003    |
| LDL-c, mmol/L            | 3.0 ± 0.5      | 3.1 ± 0.4   | 0.509    | 3.0 ± 0.5              | 0.632    | 3.0 ± 0.4               | 0.515    |
| Triglycerides, mmol/L     | 1.8 ± 0.4      | 1.8 ± 0.4   | 0.654    | 1.8 ± 0.4              | 0.253    | 1.8 ± 0.4               | 0.883    |
| Fasting glucose, mmol/L   | 4.9 ± 0.7      | 4.8 ± 0.6   | 0.209    | 4.7 ± 0.6              | 0.097    | 4.8 ± 0.6               | 0.334    |
| Na⁺, mmol/L              | 141.9 ± 2.2    | 141.2 ± 2.5 | 0.037    | 140.9 ± 2.6            | 0.016    | 141.3 ± 2.4             | 0.074    |
| K⁺, mmol/L                | 4.0 ± 0.3      | 4.0 ± 0.3   | 0.746    | 4.1 ± 0.4              | 0.009    | 4.0 ± 0.3               | 0.578    |
| LAD, mm                   | 33.9 ± 4.4     | 39.5 ± 5.7  | 0.001    | 43.0 ± 5.6             | 0.001    | 38.2 ± 5.3              | 0.001    |
| LVEDD, mm                 | 46.3 ± 4.3     | 48.0 ± 4.6  | 0.041    | 48.5 ± 4.0             | 0.014    | 47.2 ± 4.7              | 0.090    |
| LVPWT, mm                 | 9.2 ± 1.3      | 11.4 ± 1.4  | 0.001    | 11.7 ± 1.4             | 0.001    | 11.3 ± 1.3              | 0.001    |
| IVST, mm                  | 9.3 ± 1.6      | 11.6 ± 1.6  | 0.001    | 12.0 ± 1.7             | 0.001    | 11.5 ± 1.6              | 0.001    |
| LVEF, %                   | 63.0 ± 6.5     | 62.3 ± 4.8  | 0.23     | 60.5 ± 5.9             | 0.012    | 62.7 ± 4.3              | 0.664    |
| ACEIs/ARBs               | 55 (67.1%)     | 203 (58.0%) | 0.132    | 37 (48.1%)             | 0.015    | 166 (60.8%)             | 0.305    |
| Statins                  | 20 (24.4%)     | 108 (30.9%) | 0.248    | 33 (42.9%)             | 0.014    | 75 (27.5%)              | 0.661    |
| Beta-blockers            | 23 (28.0%)     | 140 (40.0%) | 0.06     | 32 (41.6%)             | 0.073    | 108 (39.6%)             | 0.058    |
| Diuretics                | 10 (12.2%)     | 50 (14.3%)  | 0.662    | 10 (13.0%)             | 0.880    | 40 (14.7%)              | 0.575    |
| CCBs                     | 33 (40.2%)     | 130 (37.1%) | 0.602    | 14 (18.2%)             | 0.002    | 116 (42.5%)             | 0.718    |
| Propafenone              | -              | 100 (28.6%) | -        | 25 (32.5%)             | -        | 75 (27.5%)              | -        |
| Amiodarone               | -              | 103 (29.4%) | -        | 28 (36.4%)             | -        | 80 (29.3%)              | -        |
| Digoxin                  | -              | 51 (14.6%)  | -        | 11 (14.3%)             | -        | 40 (14.7%)              | -        |
| Aspirin                  | 35 (42.7%)     | 175 (50.0%) | 0.233    | 37 (48.1%)             | 0.497    | 138 (50.5%)             | 0.211    |
| Anticoagulation drugs    | -              | 55 (15.7%)  | -        | 17 (22.1%)             | -        | 39 (14.3%)              | -        |
| Warfarin                 | -              | 39 (11.1%)  | -        | 10 (13.0%)             | -        | 29 (10.6%)              | -        |
| Dabigatran/Rivaroxaban   | -              | 17 (5.0%)   | -        | 7 (9.1%)               | -        | 10 (3.7%)               | -        |

Data are presented as means ± SD or n (%). ³Presented as median (interquartile range). *Refers to versus control group. ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blocking agents; BMI: body mass index; CCBs: calcium channel blockers; DBP: diastolic blood pressure; Hb: hemoglobin; HDL-c: high-density lipoprotein cholesterol; IVST: interventricular septum thickness; LAD: left atrial diameter; LDL-c: low-density lipoprotein cholesterol; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVPWT: left ventricular posterior wall thickness; RDW: red cell distribution width; SBP: systolic blood pressure; TG: total cholesterol; WBC: white blood cell.

Furthermore, the RDW concentrations in the persistent AF subgroup and presence group of the paroxysmal AF subgroup were higher than those of the control group (P = 0.001, P = 0.001, respectively) and the absence group of the paroxysmal AF subgroup (5.9 ± 1.4 vs. 5.4 ± 1.8 × 10⁹/L, P = 0.189) (Table 2).
There was no significant difference in the WBC count between the absence group of the paroxysmal AF subgroup and control group ($P = 0.189$).

### 3.3 Predictors of increased RDW concentration in hypertensive AF patients

In the univariate analysis, including age, sex, BMI, smoking, antihypertensive drugs, statin, duration of hypertension, AF rhythm, LAD, LVEDD, LVEF, IVST and LVPWT of all AF patients were analyzed. It demonstrated that LAD, statin, LVPWT and AF rhythm were associated with the RDW level.

In the multivariate analysis, the AF rhythm ($t = 4.448$, $P = 0.001$) and LVPWT ($t = -2.778$, $P = 0.006$) was independently associated with high RDW levels, respectively (Table 3).

### 4 Discussion

The present study demonstrated the independent association between AF rhythm and RDW in hypertensive patients. Among patients with essential hypertension, those with AF had elevated RDW levels compared to controls. Furthermore, the RDW levels in patients with persistent AF was similar to those of paroxysmal AF patients with AF rhythm at the time of blood sampling, both of which were higher than those of the controls and paroxysmal AF patients with a sinus rhythm at the time of blood sampling. Presence of AF rhythm was independently associated with an elevated RDW level after adjusting for other variables. Consequently, a growing body of evidence demonstrated that inflammation is implicated in the pathophysiology of atrial remodeling in AF.\[4-7\] The mechanisms link atrial remodeling and inflammation are complex; while diverse underlying diseases and conditions, including hypertension, may participate in the pathway. Inflammation indexes, including C-reactive protein, tumor necrosis factor-$\alpha$, interleukin-1 and interleukin-6, have been associated with AF initiation and perpetuation, recurrence post-catheter ablation, and even with prothrombotic states. It has been demonstrated that oxidant stress and inflammatory activation may be involved as the inter-related pathways, promoting atrial electrical and structural remodeling and leading to atrial fibrosis and increased stroke risk.

The RDW reflects the variability in the size of circulating red blood cells provided by an automatic blood count instrument that measures, in more than ten seconds, a hundred thousand red blood cell volume changes to the size of the coefficient of variation and that can accurately and timely reflect the extent of the changes in the red blood cell size. Recently, evidence suggests that high levels of RDW may reflect an activated inflammatory state. Specifically, inflammation and oxidative stress may inhibit erythrocyte maturation. Thus, immature red blood cells enter into the blood circulation and increase their relative proportion to mature red blood cells leading to the observed heterogeneity in the size. Some studies have demonstrated an association between increased RDW levels and adverse cardiovascular events in patients with heart failure, coronary artery disease, stroke and cardiovascular disease as well as the general population.\[10-14\] Recently, several published works explored the potential relationship between AF and RDW.\[19-22\] They suggested that an enhanced RDW level is not only a predictive factor and a marker of AF, but also a helpful predictor of the risk of developing adverse complications in patients with AF, such as recurrence and prolonged duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality.

The present study included the patients with essential hypertension. Previous studies have shown that inflammation plays an important role in the development of hypertension.\[8,9\] In the setting of hypertension, accumulating data demonstrated that low grade inflammation with endothelial dysfunction and activation of reni-angiotensin-aldosterone axis are implicated to the development of hypertensive target organ damage, including left atrial and ventricular myocardium. Furthermore, angiotensin II promotes persistent activation of the sympathetic nervous system, oxidant production via NADPH oxidases, cardiac hypertrophy, systemic inflammatory activation and atrial inflammatory cell infiltration, development of atrial fibrosis, gap junction uncoupling, impaired atrial $Ca^{2+}$-handling and atrial ion channel remodeling.\[23\]
Table 2. Baseline characteristics: presence versus absence of paroxysmal atrial fibrillation.

| Characteristic               | Presence of paroxysmal AF | Absence of paroxysmal AF |
|-----------------------------|---------------------------|--------------------------|
| (n = 67)                    | P-value<sup>*</sup>       | P-value<sup>**</sup>     | (n = 206)                  | P-value<sup>*</sup>       | P-value<sup>**</sup>     |
| Age, yrs                   | 57.1 ± 10.3               | 0.105                    | 0.024                      | 0.001                      | 61.8 ± 10.6               | 0.001                    | 0.468                      |
| Male                       | 58 (86.6%)                | 0.006                    | 0.438                      | 0.001                      | 119 (57.8%)               | 0.145                    | 0.001                      |
| Smoking                    | 22 (32.8%)                | 0.434                    | 0.906                      | 0.596                      | 75 (36.4%)                | 0.678                    | 0.680                      |
| Duration of hypertension, yrs | 8 (5–10)                 | 0.067                    | 0.157                      | 0.317                      | 7 (6–11)                  | 0.001                    | 0.471                      |
| BMI, kg/m²                 | 24.7 ± 1.9                | 0.217                    | 0.219                      | 0.372                      | 24.4 ± 2.4                | 0.559                    | 0.021                      |
| Office heart rate, beats/min | 88.4 ± 15.4               | 0.001                    | 0.212                      | 0.001                      | 73.6 ± 15.9               | 0.675                    | 0.001                      |
| Office SBP, mmHg           | 144.3 ± 7.0               | 0.860                    | 0.033                      | 0.533                      | 144.8 ± 5.5               | 0.163                    | 0.021                      |
| Office DBP, mmHg           | 88.2 ± 9.2                | 0.860                    | 0.010                      | 0.156                      | 90.2 ± 10.0               | 0.202                    | 0.161                      |
| WBC, ×10⁹/L               | 5.9 ± 1.4                 | 0.032                    | 0.208                      | 0.189                      | 5.4 ± 1.8                 | 0.001                    | 0.854                      |
| Hb, g/L                   | 145.1 ± 15.8              | 0.045                    | 0.080                      | 0.048                      | 140.6 ± 16.2              | 0.681                    | 0.001                      |
| RDW, %                    | 13.0 ± 0.6                | 0.001                    | 0.533                      | 0.001                      | 12.5 ± 0.9                | 0.262                    | 0.001                      |
| Creatinine, µmol/L        | 82.1 ± 13.4               | 0.029                    | 0.102                      | 0.061                      | 78.0 ± 16.7               | 0.820                    | 0.001                      |
| TG, mmol/L                | 4.9 ± 0.5                 | 0.180                    | 0.503                      | 0.881                      | 4.9 ± 0.5                 | 0.170                    | 0.355                      |
| HDL-c, mmol/L             | 1.4 ± 0.2                 | 0.016                    | 0.007                      | 0.677                      | 1.4 ± 0.2                 | 0.003                    | 0.001                      |
| LDL-c, mmol/L             | 3.0 ± 0.4                 | 0.714                    | 0.386                      | 0.169                      | 3.1 ± 0.4                 | 0.339                    | 0.735                      |
| Fasting glucose, mmol/L   | 4.8 ± 0.7                 | 0.673                    | 0.246                      | 0.633                      | 4.8 ± 0.7                 | 0.288                    | 0.335                      |
| Na⁺, mmol/L               | 141.2 ± 2.5               | 0.075                    | 0.579                      | 0.532                      | 141.4 ± 2.4               | 0.114                    | 0.168                      |
| K⁺, mmol/L                | 4.0 ± 0.3                 | 0.884                    | 0.012                      | 0.669                      | 4.0 ± 0.3                 | 0.510                    | 0.001                      |
| LAD, mm                   | 40.1 ± 4.7                | 0.001                    | 0.001                      | 0.004                      | 38.0 ± 5.4                | 0.001                    | 0.001                      |
| LVEDD, mm                 | 48.6 ± 4.6                | 0.015                    | 0.839                      | 0.107                      | 47.6 ± 4.7                | 0.227                    | 0.130                      |
| LVPTW, mm                 | 11.4 ± 1.0                | 0.001                    | 0.223                      | 0.230                      | 11.2 ± 1.4                | 0.001                    | 0.012                      |
| IVST, mm                  | 11.4 ± 1.8                | 0.001                    | 0.035                      | 0.777                      | 11.5 ± 1.5                | 0.001                    | 0.008                      |
| LVEF, %                   | 62.4 ± 4.6                | 0.530                    | 0.034                      | 0.479                      | 62.9 ± 4.2                | 0.802                    | 0.001                      |
| ACEIs/ARBs                | 46 (68.7%)                | 0.837                    | 0.013                      | 0.130                      | 120 (58.3%)               | 0.167                    | 0.124                      |
| Statins                   | 20 (29.9%)                | 0.001                    | 0.106                      | 0.543                      | 55 (26.7%)                | 0.768                    | 0.009                      |
| Beta-blockers             | 28 (41.8%)                | 0.079                    | 0.977                      | 0.234                      | 80 (38.8%)                | 0.085                    | 0.677                      |
| Diuretics                 | 11 (16.4%)                | 0.484                    | 0.586                      | 0.638                      | 29 (14.1%)                | 0.673                    | 0.813                      |
| CCBs                      | 31 (46.3%)                | 0.460                    | 0.001                      | 0.471                      | 85 (41.3%)                | 0.874                    | 0.001                      |
| Propafenone               | 20 (29.9%)                | -                        | 0.735                      | 0.616                      | 55 (26.7%)                | -                        | 0.276                      |
| Amiodarone                | 25 (37.3%)                | -                        | 0.906                      | 0.097                      | 55 (26.7%)                | -                        | 0.112                      |
| Digoxin                   | 11 (16.4%)                | -                        | 0.723                      | 0.638                      | 29 (14.1%)                | -                        | 0.964                      |
| Aspirin                   | 34 (50.7%)                | 0.326                    | 0.747                      | 0.970                      | 104 (50.5%)               | 0.232                    | 0.716                      |
| Anticoagulation drugs     | 7 (10.4%)                 | -                        | 0.091                      | 0.301                      | 32 (15.5%)                | -                        | 0.295                      |
| Warfarin                  | 4 (6.0%)                  | -                        | 0.156                      | 0.155                      | 25 (12.1%)                | -                        | 0.847                      |
| Dabigatran/Rivaroxaban    | 3 (4.5%)                  | -                        | 0.277                      | 0.683                      | 7 (3.4%)                  | -                        | 0.049                      |

Data are presented as means ± SD or n (%). <sup>*</sup>Presented as median (interquartile range). <sup>**</sup>Refers to versus control group. <sup>***</sup>Refers to versus persistent AF. <sup>***</sup>Refers to versus absence of AF group. ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blocking agents; BMI: body mass index; CCBs: calcium channel blockers; DBP: diastolic blood pressure; Hb: hemoglobin; HDL-c: high-density lipoprotein cholesterol; IVST: interventricular septum thickness; LAD: left atrial diameter; LDL-c: low-density lipoprotein cholesterol; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVPWT: left ventricular posterior wall thickness; RDW: red cell distribution width; SBP: systolic blood pressure; TG: total cholesterol; WBC: white blood cell.
Table 3. Univariate and multivariate analysis results for elevated RDW levels in patients with atrial fibrillation with hypertension.

| Variable                                | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                         | β       | t       | P-value | β       | t       | P-value |
| Age, yrs                                | −0.059  | −1.095  | 0.274   | −0.018  | −0.323  | 0.747   |
| Male                                    | 0.017   | 0.208   | 0.745   | 0.019   | 0.291   | 0.772   |
| Smoking                                 | 0.095   | 1.691   | 0.092   | 0.087   | 0.585   | 0.114   |
| BMI, kg/m²                               | 0.048   | 0.893   | 0.373   | −0.014  | −0.270  | 0.787   |
| Duration of hypertension, yrs           | 0.027   | 0.505   | 0.614   | 0.011   | 0.198   | 0.843   |
| Office heart rate, beats/min            | 0.076   | 1.425   | 0.155   | −0.026  | −0.460  | 0.646   |
| Office SBP, mmHg                        | 0.039   | 0.728   | 0.467   | 0.039   | 0.739   | 0.460   |
| Office DBP, mmHg                        | 0.061   | 1.144   | 0.253   | 0.057   | 1.083   | 0.280   |
| AF rhythm                               | 0.262   | 5.061   | 0.001   | 0.276   | 4.448   | 0.001   |
| Creatinine, μmol/L                     | −0.062  | −1.165  | 0.245   | −0.091  | 1.443   | 0.150   |
| LAD, mm                                 | 0.134   | 2.520   | 0.012   | 0.106   | 1.809   | 0.071   |
| LVEDD, mm                               | 0.041   | 0.770   | 0.442   | 0.011   | 0.212   | 0.833   |
| LVEF, %                                 | −0.080  | −1.499  | 0.138   | −0.017  | −0.312  | 0.755   |
| IVST, mm                                | −0.096  | −1.802  | 0.072   | −0.094  | −1.693  | 0.091   |
| LVPWT, mm                               | −0.147  | −2.770  | 0.006   | −0.156  | −2.778  | 0.006   |
| Statins                                 | 0.108   | 2.026   | 0.043   | 0.065   | 1.191   | 0.234   |
| ACEIs/ARBs                              | 0.014   | 0.263   | 0.793   | −0.005  | −0.085  | 0.933   |
| Beta-blockers                           | −0.009  | −0.165  | 0.869   | −0.043  | −0.803  | 0.423   |
| Diuretics                               | −0.011  | −0.196  | 0.844   | 0.039   | 0.621   | 0.535   |
| CCBs                                    | −0.065  | −1.223  | 0.222   | −0.037  | −0.601  | 0.548   |
| Aspirin                                 | 0.047   | 0.883   | 0.378   | 0.053   | 0.890   | 0.374   |
| Anticoagulation drugs                   | 0.004   | 0.082   | 0.935   | −0.008  | −0.137  | 0.891   |

ACEIs: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blocking agents; BMI: body mass index; CCBs: calcium channel blockers; DBP: diastolic blood pressure; IVST: interventricular septum thickness; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVPWT: left ventricular posterior wall thickness; RDW: red cell distribution width; SBP: systolic blood pressure.

The RDW level is increased in hypertensive patients, especially in those with non-dipper hypertension.[15,24] Anisocytosis, mainly resulting from the ongoing vascular inflammation, is correlated with complications of essential hypertension, especially with an abnormal left ventricular geometric pattern. Hypertension is major risk factor for AF and is often accompanied by underlying cardiovascular disease or other metabolic abnormalities, such as diabetes or metabolic syndrome.[2,3] Thus, to avoid the potential effects of these abnormal situations on the RDW level, the patients with other cardiovascular disorders were excluded.

The present study further explored the relationship between AF and RDW in hypertensive patients. Patients with paroxysmal AF had transient elevation of RDW levels, which returned to baseline level after the reversion to sinus rhythm. Moreover, in the multivariate logistic regression, the AF rhythm was independently related to the elevated RDW level. Previous studies have shown that the presence of anisocytic erythrocytes was involved in the mechanisms underlying adverse cardiac remodeling,[25] thus leading to atrial fibrosis and predisposing the patients to a higher risk of developing AF.[26] Combined with our study, the relatively increased RDW concentrations during the AF rhythm may demonstrate the involvement of RDW in the inflammatory reaction of the atrial myocardium and the myocardial tissue damage. In this sense, in hypertensive AF patients, effective treatment of the maintenance of sinus rhythm may be of great importance for the attenuation of the atrial remodeling.

There is limited information about the relationship between RDW and AF in hypertension.[17] Our study confirms that the RDW levels were higher in hypertensive patients with AF than in those without AF, which is consistent with the finding of the previous study.[17] More importantly, our
work further explored the different RDW levels of the controls, persistent AF patients and paroxysmal AF patients with and without AF rhythm at the time of blood sampling. It is believed that these results further improve the knowledge of the association between RDW and AF in hypertensive patients.\textsuperscript{[27]}

4.1 Limitations

Although our results indicate a possible association between RDW and AF in hypertensive patients, it still had a limitation. The present study did not have a prospective cohort design, which hindered the determination of the cause-effect relationship between inflammation and AF. Thus, it remains controversial whether inflammation was the cause or the consequence of AF. Further studies on this matter are warranted in the future.

4.2 Conclusions

This study demonstrated that, in patients with hypertension, the inflammation indexed by RDW is significantly related to AF. Moreover, the presence of AF rhythm is independently associated with elevated RDW levels.

Acknowledgments

This study was supported by the National Natural Scientific Foundation of China (No.81600275). All authors had no conflicts of interest to disclose.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983–988.
2. Benjamin EJ, Wolf PA, D’Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98: 946–952.
3. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N–9N.
4. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003; 108: 3006–3010.
5. Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: post-surgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997; 96: 3542–3548.
6. Lazzerini PE, Laghi-Pasini F, Acampa M, et al. Systemic inflammation rapidly induces reversible atrial electrical remodeling: the role of interleukin-6-mediated changes in connexin expression. J Am Heart Assoc 2019; 8: e011006.
7. Zheng LH, Sun W, Yao Y, et al. Associations of big endothelin-1 and C-reactive protein in atrial fibrillation. J Geriatr Cardiol 2016; 13: 465–470.
8. Androulakis ES, Tousoulis D, Papageorgiou N, et al. Essential hypertension: is there a role for inflammatory mechanisms? Cardiol Rev 2009; 17: 216–221.
9. Guiuva’c’h E, Favre J, Guihot AL, et al. Nuclear activation function 2 estrogen receptor α attenuates arterial and renal alterations due to aging and hypertension in female mice. J Am Heart Assoc 2020; 9: e013895.
10. Felker GM, Allen LA, Pocock SJ, et al. 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.
11. Aung N, Ling HZ, Cheng AS, et al. Expansion of the red cell distribution width and evolving iron deficiency as predictors of poor outcome in chronic heart failure. Int J Cardiol 2013; 168: 1997–2002.
12. Tonelli M, Sacks F, Arnold M, et al. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation 2008; 117: 163–168.
13. Benedetto U, Angeloni E, Melina G, et al. Red blood cell distribution width predicts mortality after coronary artery bypass grafting. Int J Cardiol 2013; 165: 369–371.
14. Cavusoglu E, Chopra V, Gupta A, et al. Relation between red blood cell distribution width (RDW) and all-cause mortality at two years in an unselected population referred for coronary angiography. Int J Cardiol 2010; 141: 141–146.
15. Ozcan F, Turak O, Durak A, et al. Red cell distribution width and inflammation in patients with non-dipper hypertension. Blood Press 2013; 22: 80–85.
16. Emans ME, Gaillard CA, Pfister R, et al. Red cell distribution width is associated with physical inactivity and heart failure, independent of established risk factors, inflammation or iron metabolism; the Epic-Norfolk study. Int J Cardiol 2013; 168: 3550–3555.
17. Sarikaya S, Şahin Ş, Akylol L, et al. Is there any relationship between RDW levels and atrial fibrillation in hypertensive patient? Afr Health Sci 2014; 14: 267–272.
18. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893–2962.
19. Liu T, Shao Q, Miao S, et al. Red cell distribution width as a novel, inexpensive marker for paroxysmal atrial fibrillation. Int J Cardiol 2014; 171: e52–e53.
20. Lee KH, Park HW, Cho JG, et al. Red cell distribution width as a novel predictor for clinical outcomes in patients with paroxysmal atrial fibrillation. Europace 2015; 17: i83–i88.
21. Yanagisawa S, Inden Y, Kato H, et al. 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. Circ J 2016; 80: 627–638.
22 Cha MJ, Lee HS, Kim HM, et al. Association between red cell distribution width and thromboembolic events in patients with atrial fibrillation. *Eur J Intern Med* 2017; 46: 41–46.
23 Rudolph V, Andrié RP, Rudolph TK, et al. Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation. *Nat Med* 2010; 16: 470–474.
24 Tanindi A, Topal FE, Topal F, et al. Red cell distribution width in patients with prehypertension and hypertension. *Blood Press* 2012; 21: 177–181.
25 Fujii T, Nishigaki R, Kawahara K, et al. Ultrastructural changes and immunohistochemical localization of advanced glycation end products in the heart of streptozotocin-treated Mongolian gerbils. *Med Electron Microsc* 1999; 32: 43–49.
26 Shimano M, Tsuji Y, Inden Y, et al. Pioglitazone, a peroxisome proliferator-activated receptor-gamma activator, attenuates atrial fibrosis and atrial fibrillation promotion in rabbits with congestive heart failure. *Heart Rhythm* 2008; 5: 451–459.
27 Tsioufis C, Syrseloudis D, Hatziyianni A, et al. Relationships of CRP and P wave dispersion with atrial fibrillation in hypertensive subjects. *Am J Hypertens* 2010; 23: 202–207.