High red blood cell distribution width is closely associated with risk of carotid artery atherosclerosis in patients with hypertension

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BACKGROUND: A high red blood cell distribution width (RDW) may be associated with adverse outcomes in patients with heart failure and risk of death, and cardiovascular events in people with previous myocardial infarction. Ultrasound detection of carotid plaque helps to identify asymptomatic patients with advanced subclinical atherosclerosis, which can predict risk of cardiovascular death or myocardial infarction. However, the relationship of RDW and carotid artery atherosclerosis in hypertensive people is less certain.
OBJECTIVE: To evaluate the association between RDW and carotid artery atherosclerosis in people with hypertension.
METHODS: RDW was determined using a Coulter counter together with white blood cell count in 156 hypertensive inpatients 60 to 85 years of age. Carotid intimal-medial thickness (IMT) and carotid atherosclerotic plaques were identified by ultrasound imaging. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels were determined using a multichannel analyzer. Systolic and diastolic blood pressures were measured manually.
RESULTS: The number of patients with carotid artery atherosclerotic plaque, as well as the carotid IMT to inner diameter ratio, were significantly different among the different RDW groups of hypertensive inpatients ($P<0.01$). With linear regression analysis, increased carotid IMT and higher white blood cell count were identified to be significant and independent contributors to the RDW of hypertensive inpatients ($P<0.05$).
CONCLUSIONS: A close relationship between high RDW and IMT, and the incidence of carotid plaque, was identified in 156 hypertensive inpatients.

Key Words: *Carotid intimal-medial thickness; Hypertension; Red blood cell distribution width*

Red blood cell distribution width (RDW) is a numerical measure of the size variability of circulating erythrocytes and is routinely reported as a component of complete blood count in the differential diagnosis of anemia. RDW has been very recently reported to be a strong and independent predictor of adverse outcomes in the general population (1,2). Increased RDW is also believed to be closely associated with the risk of cardiovascular morbidity and mortality in patients with previous myocardial infarction (3). Ultrasound detection of carotid plaque and carotid intimal-medial thickness (IMT) in asymptomatic patients is often related to advanced subclinical atherosclerosis, a risk of cardiovascular death and/or myocardial infarction (4,5). However, the association between RDW and carotid artery atherosclerosis has not been explored. We assessed the relationship between RDW and the incidence of carotid atherosclerotic plaques, and carotid IMT, in 156 subjects with hypertension.

METHODS

Study subjects

The protocol of the present study was reviewed and approved by the Ethics and Research Committee of the Navy General Hospital (Beijing, China). The study population gave informed consent before carotid ultrasound imaging examination and blood sampling.

The overall study population consisted of 156 hypertensive inpatients 60 to 85 years of age, who were admitted to the hospital for a health examination between 2007 and 2008. Patients with complete, available medical records were selected according to the following inclusion and exclusion criteria; their demographic and clinical data are shown in Table 1. Patients included in the study had well-controlled hypertension (diastolic blood pressure of less than 90 mmHg and systolic blood pressure of less than 150 mmHg), were taking antihypertensive medication, and had taken acetylsalicylic acid (100 mg/day). Exclusion criteria included the presence of hematological system diseases, diabetes mellitus and cerebral infarction (except lacunar infarction); any systemic disease, such as hemolytic, hepatic and renal diseases; or other diseases that could affect white blood cells, red blood cells or hemoglobin. The diagnostic criteria for coronary artery disease included the previous onset of myocardial infarction or more than 75% narrowing of the coronary artery, as determined by radiography.

Carotid ultrasound imaging

Carotid ultrasound, followed by a duplex colour Doppler examination, was performed on the patients in the supine position, with a Phillips ATL 5000 ultrasound system (ATL, Poland) using a linear probe at a frequency of 7.5 MHz to

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TABLE 1
Baseline characteristics of the different red blood cell distribution width (RDW) groups of hypertensive inpatients

	Lowest (n=30)	Low (n=41)	High (n=36)	Highest (n=49)	P
RDW, %	11.02±0.48	12.04±0.15	13.06±0.16	15.00±1.14	
Demographic characteristics and comorbidity					
Age, years	77±9.59	74±10.24	72±11.54	74±9.84	0.282
Women, n	4	4	6	6	0.000
History of hypertension, years	12.2±12.4	19.1±18.1	11.4±10.3	13.7±13.0	0.210
Coronary artery disease, n	7	17	11	11	0.000
IMT/ID, $\times 10^{-2}$	6.70±4.17	7.76±3.12	8.56±2.83	10.96±1.83	0.000
Carotid plaque, n	13	19	17	27	0.000
Medication use, n					
Simvastatin	9	14	15	21	0.000
Beta-adrenergic blocker	5	10	8	10	0.000
Angiotensin-converting enzyme inhibitor	12	21	19	25	0.000
Calcium channel blocker	25	34	33	41	0.000
Thiazide diuretic	18	28	24	38	0.000
Lipid status, mmol/L					
Total cholesterol	4.24±1.06	4.50±0.83	4.32±1.01	4.43±0.88	0.658
LDL cholesterol	3.21±0.63	3.47±0.87	3.37±1.11	3.51±0.93	0.714
HDL cholesterol	1.12±0.36	1.10±0.23	1.11±0.33	1.11±0.27	0.999
Triglycerides	1.51±1.01	1.37±0.72	1.41±1.03	1.44±1.09	0.938
Blood pressure, mmHg					
Systolic	133±15.66	133±18.04	131±17.90	140±18.60	0.071
Diastolic	72±10.06	72±8.80	75±17.53	78±10.59	0.087
Laboratory parameters					
Hemoglobin, g/L	13.25±0.34	13.00±0.22	12.86±0.47	12.81±1.19	0.056
White blood cell count, $\times 10^9$/L	5.90±1.41	6.16±1.69	6.23±0.97	7.56±1.20	0.000

Data are presented as mean ± SD unless otherwise indicated. HDL High-density lipoprotein; IMT/ID Ratio of intimal-medial thickness to inner diameter; LDL Low-density lipoprotein

12 MHz. Both left and right common carotid arteries were analyzed. Multiple measurements of the distal wall from anterior, lateral and posterior longitudinal projections were recorded. Maximal IMT was measured in two segments of 1 cm each, from the beginning of the common carotid bulb. The IMT value was calculated as the arithmetical mean of the bulb and common carotid segment measurements of both sides. To control for natural size variation of the carotid artery among individuals, the ratio of IMT to inner diameter (ID) was used for statistical analysis. Carotid plaque was defined as an echogenic thickening of intimal reflection that encroaches on the arterial lumen, with a minimal IMT of greater than 1.2 mm, as previously described by Zweibel (6) in 2000 and Li et al (7) in 1996. Plaques were characterized simply as 'present' or 'absent'.

Measurement of RDW and laboratory parameters

The blood samples were drawn from participating patients after an overnight fast of more than 12 h. The RDW, hemoglobin level, white blood cell count and mean corpuscular volume were determined using a Model S-PLUS JR Coulter Counter (Beckman Coulter Inc, USA), with a Coulter histogram differential count as part of the complete blood cell count. The serum levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides were measured using a multichannel analyzer (Roche Hitachi 737; Boehringer Mannheim Diagnostics, USA). Baseline RDW was measured as a continuous variable and the data were divided into four categories accordingly (lowest: 11% to less than 12%; low: 12% to less than 13%; high: 13% to less than 14%; highest: 14% or greater).

Other factors

The patients' age, sex, history of hypertension, coronary artery disease and medication use, such as simvastatin, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers and thiazide diuretics, were recorded. Blood pressure was measured in the right arm using a mercury sphygmomanometer after 20 min of rest with the patient in a sitting position.

Statistical analysis

Data were expressed as mean ± SD or counts. Statistical analysis was performed using SPSS version 12.0 (SPSS Inc, USA), and the level of statistical significance was defined as $P<0.05$. There were no significant differences between left and right IMT/ID ratio. Therefore, data are presented as the mean values of left and right IMT/ID ratio. The χ^2 test or one-way ANOVA was used for continuous factors between different categories of RDW. Multivariate linear regression was used to determine the factors that were associated with baseline RDW.

RESULTS

Baseline characteristics

All 156 patients were evaluated at baseline and found to be eligible for the present analysis. The demographic characteristics of these people are summarized in Table 1. RDWs ranged from 10.00% to 19.00% (median 13.01%).

Patients with higher RDWs tended to be men and were more likely to have coronary artery disease, carotid plaque, a high white blood cell count, a high IMT/ID ratio and low hemoglobin levels. Other factors that were independently associated with baseline RDW are shown in Table 2.

Association between RDW and IMT, and carotid plaque

A high baseline RDW was observed in patients with an increased IMT/ID ratio (95% CI 4.54 to 28.59; $P=0.008$; Table 2). When the participants were divided into four categories based on their RDW, a significant difference ($P<0.01$) was identified between carotid artery atherosclerotic plaque and carotid IMT/ID ratio in the hypertensive inpatients of different RDW categories (Table 1).

Association between RDW and white blood cell count and hemoglobin

A high baseline RDW was found to be associated with hemoglobin level ($P<0.05$; Table 2) and white blood cell count. The latter was also significantly different among the RDW groups ($P<0.01$; Table 1).

TABLE 2
Factors associated with higher levels of red blood cell distribution width as determined by multivariable linear regression analysis

						95% CI	
	B	SE	Beta	*t*	P	Lower	Upper
Age, years	0.009	0.021	0.052	0.408	0.685	–0.033	0.050
IMT/ID, $\times 10^{-2}$	16.569	5.999	0.335	2.762	0.008	4.547	28.591
History of hypertension, years	–0.006	0.017	–0.047	–0.361	0.719	–0.041	0.028
Systolic blood pressure, mmHg	0.013	0.011	0.143	1.183	0.242	–0.009	0.034
Diastolic blood pressure, mmHg	0.002	0.022	0.016	0.108	0.914	–0.041	0.046
White blood cell count, $\times 10^9$/L	0.344	0.141	0.305	2.443	0.018	0.062	0.626
Total cholesterol, mmol/L	0.050	0.238	0.025	0.212	0.833	–0.427	0.528
Triglycerides, mmol/L	0.130	0.174	0.085	0.748	0.458	–0.218	0.478
LDL cholesterol, mmol/L	–0.151	0.240	–0.083	–0.630	0.531	–0.632	0.330
HDL cholesterol, mmol/L	–0.528	0.708	–0.083	–0.745	0.459	–1.948	0.892
Hemoglobin, g/L	–0.573	0.256	–0.254	–2.237	0.029	–1.086	–0.060

HDL High-density lipoprotein; IMT/ID Ratio of intimal-medial thickness to inner diameter; LDL Low-density lipoprotein

DISCUSSION

RDW reflects variability in the size of circulating red blood cells (anisocytosis) and is routinely reported by automated blood counts in laboratories. Its inclusion in the complete blood count has made diagnosing certain anemias easier, especially those that are microcytic (caused by iron deficiency), and those due to vitamin B_{12} or folic acid deficiencies. An increased RDW can also result from conditions that modify the shape of red blood cells due to the premature release of immature cells into the bloodstream (severe blood loss), abnormal hemoglobins (eg, sickle cell anemia), hemolysis or hemolytic anemias (8,9).

The recent prospective evidence of a strong association between elevated RDW and the occurrence of chronic heart failure, as well as fatal and nonfatal cardiovascular disease events, has revealed a new and unpredictable scenario in the clinical usefulness of RDW. Given the fact that RDW is widely available to clinicians as a part of the complete blood count and thus incurs no additional costs, the diagnostic value of RDW in cardiovascular diseases should not be underestimated when compared with other novel prognostic markers of the disease.

Common carotid IMT as measured by ultrasonography represents a marker of structural atherosclerosis. Increased carotid IMT has been shown to be correlated with cardiovascular disease risk (10) and severity of coronary atherosclerosis (11), and is helpful in predicting cardiovascular disease events in population groups (12,13). Increased carotid IMT is considered to be an early phase of atherosclerosis, and might be seen even in patients with mild hypertension and normal serum cholesterol (14). Assessment of carotid IMT using high-resolution B-mode ultrasonography is a reliable, reproducible and noninvasive method for detecting and monitoring the progression of atherosclerosis (15).

In the present study, we identified a graded and independent association of baseline RDW with the IMT/ID and incidence of carotid plaque, which is similar to that observed in patients with pre-existing cardiovascular disease (3). Although the exact physiological mechanisms that underlie the association of RDW with carotid artery atherosclerosis are unknown, systemic factors that alter erythrocyte homeostasis, such as inflammation and oxidative stress, likely play a role. It has been demonstrated that inflammation and oxidative stress are involved in arterial atherosclerosis (16,17). Inflammation might contribute to an increased RDW by not only impairing iron metabolism but also by inhibiting the production of or response to erythropoietin, or by shortening red blood cell survival (18,19). Using an index comprised of multiple proinflammatory cytokines, Ferrucci et al (20) showed that higher levels of inflammation were associated with higher erythropoietin concentration among nonanemic older adults, whereas an inverse association was observed in anemic persons. This suggests that, in a proinflammatory state, the increase in erythropoietin is a compensatory mechanism for maintaining normal hemoglobin concentration. Anemia occurs when the compensatory increment in erythropoietin production in unsustainable. Lippi et al (21) reported a graded association of RDW with high-sensitivity C-reactive protein and erythrocyte sedimentation rate independent of numerous confounding factors. From our study, high white blood cell count as an indicator of inflammation was positively related to RDW, suggesting a role for inflammation in increasing RDW.

In addition to inflammation, oxidative stress might also contribute importantly to anisocytosis. While erythrocytes have tremendous antioxidant capacity and serve as the primary 'oxidative sink', they are prone to oxidative damage that reduces cell survival (22). In a population-based study (23), higher RDW values were independently associated with poorer pulmonary function – a condition associated with oxidative stress.

It remains to be determined, however, whether RDW is a simple marker, rather than a mediator of carotid artery atherosclerosis. Identification of a putative causative mechanism is, in fact, hampered by the lack of epidemiological studies that demonstrate an association between atherosclerosis and anisocytosis. A limitation of the present study is that few data were collected and, therefore, the mechanisms that underlie the association of RDW with carotid artery atherosclerosis remain to be determined in a large-scale study.

SUMMARY

We made the novel observation that a high RDW is strongly and independently associated with IMT and the incidence of carotid plaque. These results suggest that the study of anisocytosis might yield important pathophysiological insights, and that RDW may contribute to arterial atherosclerosis.

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