Relationship between the Red Cell Distribution Width and the One-year Outcomes in Chinese Patients with Stable Angina Pectoris

Hairong Ren, Qi Hua, Meiyan Quan, Huimin Chen, Haixia Hou, Lichao Wang, Rongkun Liu and Zheng Yang

Abstract

Objective  This study was undertaken to determine the relationship between the red cell distribution width (RDW) and the one-year outcomes in Chinese patients with stable angina pectoris.

Methods  A total of 1,442 patients with stable angina pectoris on admission were divided into four groups according to quartiles of the baseline RDW. The relationships between the RDW and one-year cardiac mortality as well as the incidence of acute coronary syndrome (ACS) were assessed.

Results  Higher RDW values were associated with an increased one-year cardiac mortality (quartile 1: 0.51%; quartile 2: 0.56%; quartile 3: 0.86%; quartile 4: 2.27%; p<0.001) and one-year ACS (quartile 1: 1.55%; quartile 2: 1.96%; quartile 3: 2.89%; quartile 4: 3.70%; p<0.001). A logistic regression analysis revealed that the RDW independently predicted cardiac mortality (OR: 1.544, 95% CI: 1.058-3.216, p<0.001) and ACS (OR: 1.861, 95% CI: 1.226-3.487, p<0.001) during a one-year follow-up in patients with stable angina pectoris.

Conclusion  The present study indicates that an elevated RDW value is associated with an increased risk of one-year adverse outcomes in patients with stable angina pectoris.

Key words: red cell distribution width, stable angina pectoris, acute coronary syndrome, cardiac mortality

(Intern Med 52: 1769-1774, 2013)
(.DOI: 10.2169/internalmedicine.52.9314)

Introduction

The red cell distribution width (RDW), an estimate of the variation in erythrocyte size, has historically been used to differentiate between types of anemia. In recent years, studies have shown that the RDW is associated with mortality in many populations, such as patients with coronary artery disease, heart failure or strokes (1-3).

The RDW has attracted attention as a marker in patients with coronary artery disease and has been reported to be a predictor of mortality in patients referred for coronary angiography (4) and patients with acute coronary syndromes (ACS) (5). Because chronic stable angina is the most common clinical manifestation of ischemic heart disease, affecting as many as 54 million people globally, it is necessary and urgent to improve the current situation (6). On the other hand, the incidence of ACS in patients with stable angina pectoris is approximately 2-3% each year on average. However, the relationship between stable angina pectoris and the RDW has not been described. At the same time, the relationship between the prognosis of patients with stable angina pectoris and the RDW has also been neglected, especially in Chinese populations. In this study, we investigated the association between the RDW and the risk of one-year mortality and ACS in Chinese patients with stable angina pectoris.
Materials and Methods

Study population

Between October 2008 and September 2011, 1,442 consecutive patients (895 men and 547 women) with stable angina pectoris admitted to our institute were enrolled in this study. The study protocol was reviewed and approved by the ethics committee of Xuanwu Hospital. Informed consent was obtained from all participating subjects. Detailed medical histories were acquired using structured interviews. The subjects were interviewed by experienced physicians using a standard questionnaire gathering information on age, smoking history, medical history of hypertension or diabetes or dyslipidemia and use of antihypertensive, antidiabetic or antihyperlipidemic medications, medical history of severe arrhythmia (including atrial fibrillation, ventricular tachycardia, frequent premature ventricular contractions and second and third degree atrioventricular block), and basic drug treatment including antiplatelet agents, nitrates, beta-blockers, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin receptor blockers (ARBs) and statins. The same weight machine, height scale and blood pressure recorder were used for the entire study population. Experienced medical staff performed the physical examinations.

The inclusion criteria were as follows: all subjects had confirmed cases of current stable angina pectoris defined as a typical clinical history with symptoms occurring within the last month and at least one area of stenosis ≥50% in more than one major epicardial coronary artery on coronary angiography.

The exclusion criteria were as follows: a history of anemia or blood transfusions; current ACS patients and patients with a history of ACS; acute or chronic heart failure; neoplastic, renal, liver, blood or thyroid disease; patients receiving treatment with anti-inflammatory drugs; patients with acute or chronic infections or autoimmune disease.

Collection and assessment of biomarkers and anthropometric data

A special questionnaire was used to collect information on lifestyle and environmental factors and medical history. Diabetes mellitus was defined as a previous diagnosis, use of diet or antidiabetic therapy or a fasting venous blood glucose level of ≥126 mg/dL on two occasions in previously untreated patients. Patients who received medications for hypertension and those with a seated systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg on at least three separate clinic visits were also identified. Patients who reported smoking at least one cigarette per day for at least one year were defined as current smokers. All subjects were asked to fast for at least 12 hours and avoid alcohol intake for at least three days before blood sampling. All anthropometric data were measured before the blood samples were drawn. The anthropometric data included body height in centimeters, weight in kilograms and BMI. The BMI was calculated as the weight in kilograms divided by the height in meters squared. The blood samples were drawn in the morning after 12 hours of fasting to determine the levels of the following parameters using standard biochemical techniques: RDW, serum uric acid, glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST), serum creatinine, blood urea nitrogen (BUN), fasting blood glucose, total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), brain natriuretic peptide (BNP) and high-sensitivity C-reactive protein (hs-CRP). The normal reference range for the RDW in this laboratory is 0.0% to 15.0%. The routine blood tests and all biochemistry measurements were performed by our biochemistry department using standard methods. The left ventricular ejection fraction (LVEF) was measured using Doppler echocardiography during the three days after admission.

Study endpoints

All patients were followed up for up to one year after discharge using a standardized protocol that included outpatient visits, telephone contact and recording of cardiac events. The primary end point was cardiac death and the secondary end point was admission for treatment of ACS. Death was classified as cardiac if the predominant and immediate cause was related to myocardial infarction (MI) or ischemia, arrhythmia, refractory congestive heart failure or sudden death. ACS included ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA). The diagnostic criteria for STEMI were as follows: 1) typical, prolonged chest pain at rest (>30 minutes); 2) ST-segment elevation ≥0.2 mV at the J point in two or more contiguous, precordial leads or ≥0.2 mV in two or more adjacent limb leads on a standard 12-lead electrocardiogram (ECG); 3) increased serum markers of myocardial damage [≥2-fold increase over the upper normal range required for creatine kinase (CK) and troponin-1 (TnI)] (7). UA/NSTEMI was defined according to the presence of ECG ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation in an appropriate clinical setting (chest discomfort or anginal equivalent) (8).

Statistical analysis

The study population was divided into four groups according to quartiles of the baseline RDW. The lowest quartile served as the reference group. The data are expressed as the means ± standard deviation (SD) for normally distributed variables. Non-normally distributed variables are expressed as the median and interquartile ranges. The qualitative data are presented as numbers (percentages). Comparisons of the data among the four groups were made using a one-way ANOVA or the Kruskal-Wallis test for continuous
variables and the chi-square test for categorical variables. The correlations between the RDW and other biochemistry parameters were assessed using Spearman’s rank correlations test for continuous variables with a non-normal distribution, and a logistic regression analysis was used to assess the relationship between the RDW and the one-year adverse outcomes of the patients with stable angina pectoris. The logistic regression analysis was adjusted for the RDW categorized according to quartiles of distribution, an age >60 years, gender, history of hypertension, diabetes or arrhythmia, the smoking status, BMI, blood pressure, the levels of serum creatinine, fasting glucose, lipids, ALT, AST, hs-CRP and hemoglobin, number of diseased vessels ≥2, a BNP level of >100 pg/mL, the white blood cell count, an LVEF of <40% and medical therapy (antiplatelet agents, nitrates, beta-blockers, ACE-Is/ARBs, CCBs, statins). The reasons for using particular threshold values, such as an age >60 years, number of diseased vessels ≥2, a BNP level of >100 pg/mL and an LVEF of <40% are as follows: in China, we still use 60 years of age as the standard for “elderly”; we selected the number of diseased vessels ≥2 because the number of diseased blood vessels affects the prognosis of patients with stable angina pectoris; in China, a diagnosis of heart failure is excluded for a BNP level of <100 pg/mL and an LVEF of <40%, and systolic heart failure is diagnosed above these values. A value of p<0.05 was considered to be statistically significant. The data management and analyses were performed using the SPSS 13.0 software package (SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics of the entire study population

Compared with the control subjects, the patients with higher RDW values were significantly older (p<0.001) and more likely to have a history of hypertension (p<0.001) or diabetes mellitus (p<0.001) and to be current smokers (p<0.001). Meanwhile, there were significantly higher levels of blood pressure (p<0.001), creatinine (p<0.001), TG (p<0.05), hs-CRP (p<0.001) and BNP (p<0.001) in the patients with higher RDW values. These patients also had lower levels of hemoglobin (p<0.001) and LVEF (p<0.001). However, there were no significant differences in gender, history of arrhythmia, BMI, heart rate, the levels of ALT, AST, BUN, TC, HDL-C, LDL-C and fasting glucose, the WBC count, number of diseased major epicardial coronary arteries ≥2 or use of antiplatelet agents, nitrates, β-blockers, ACE-Is/ARBs, CCBs and statins between the four groups. The clinical characteristics of the patients according to quartiles of the baseline RDW are presented in Table 1.

Correlations between the RDW and other biochemistry markers

Among the entire study population, using the RDW as a continuous variable, there was a correlation between the RDW and log (BNP) (r=0.230, p<0.001). The correlation coefficient between the RDW and log (hs-CRP) was 0.147 (p<0.001). The correlations between the RDW and other biochemistry markers are presented in Table 2.

Relationship between the RDW and cardiac mortality at 1 year

Follow-up information was available for 1,416 (98.1%) of the 1,442 stable angina pectoris patients at one year. There was a total of 15 deaths (1.04%) classified as cardiac in etiology. Cardiac death was more likely to occur in patients with higher RDW values (quartile 1: 0.51%; quartile 2: 0.56%; quartile 3: 0.86%; quartile 4: 2.27%; p<0.001). More details are presented in Table 3. Following multivariable adjustment for other important covariates mentioned above, the variables remaining in the equation were an LVEF of <40%, diabetes, arrhythmia, a BNP level of >100 pg/mL, an age >60 and the RDW (quartiles). Using the baseline RDW as a categorical variable according to quartiles, the adjusted odds ratio for increased cardiac mortality was 1.544 (95% CI: 1.058-3.216, p<0.001). Meanwhile, an LVEF of <40% (OR: 3.266, 95% CI: 1.088-7.432, p<0.001), diabetes (OR: 2.701, 95% CI: 1.147-5.012, p<0.001), arrhythmia (OR: 2.631, 95% CI: 1.233-4.582, p=0.030), a BNP level of >100 pg/mL (OR: 2.568, 95% CI: 1.330-4.138, p<0.001) and an age>60 (OR: 1.809, 95% CI: 1.084-3.792, p<0.001) were identified as significant independent predictors of cardiac mortality according to a logistic regression analysis (Table 4).

Discussion

Predicting the short- and long-term of risks in patients with stable angina pectoris is a challenging clinical problem. In our study, we hypothesized that inflammatory and neurohumoral activation may form a mechanistic link between a higher RDW value and a poor prognosis in Chinese patients.
Table 1. Baseline Characteristics of Study Population, Mean±SD, Number (%), or Median (Interquartile Range)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RDW quartiles</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(y)</td>
<td>≤11.7 (n=387)</td>
<td>11.8-12.5 (n=357)</td>
</tr>
<tr>
<td>Gender(male)</td>
<td>240(62.1%)</td>
<td>225(63.0%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>127(32.7%)</td>
<td>106(29.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>201(52.0%)</td>
<td>197(55.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48(12.5%)</td>
<td>63(17.6%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>27(7.1%)</td>
<td>24(6.8%)</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>218(7.1%)</td>
<td>23.62±2.88</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>104.62±7.71</td>
<td>114.58±8.20</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>66.26±5.67</td>
<td>71.75±4.86</td>
</tr>
<tr>
<td>Heart rate(beats/min)</td>
<td>68.00±9.34</td>
<td>68.33±12.69</td>
</tr>
<tr>
<td>ALT(IU/L)</td>
<td>70.41±16.83</td>
<td>73.80±15.26</td>
</tr>
<tr>
<td>TC(mmol/L)</td>
<td>4.09±0.82</td>
<td>4.17±0.75</td>
</tr>
<tr>
<td>TG(mmol/L)</td>
<td>1.38±0.38</td>
<td>1.62±0.29</td>
</tr>
<tr>
<td>HDL-cholesterol(mmol/L)</td>
<td>1.33±0.34</td>
<td>1.27±0.30</td>
</tr>
<tr>
<td>LDL-cholesterol(mmol/L)</td>
<td>2.17±0.75</td>
<td>2.16±0.57</td>
</tr>
<tr>
<td>Fasting glucose(mmol/L)</td>
<td>5.16±0.56</td>
<td>5.18±0.52</td>
</tr>
<tr>
<td>BNP(pg/mL)</td>
<td>61.90±34.201</td>
<td>59.2(1.17-186)</td>
</tr>
<tr>
<td>hs-CRP(mg/L)</td>
<td>1.06(0.01-6.21)</td>
<td>1.45(0.07-5.80)</td>
</tr>
<tr>
<td>WBC(109/L)</td>
<td>5.95±1.45</td>
<td>5.81±1.23</td>
</tr>
<tr>
<td>Hemoglobin(g/L)</td>
<td>155(10.9±87)</td>
<td>143.84±8.59</td>
</tr>
<tr>
<td>LVEF(%)</td>
<td>63.34±9.00</td>
<td>63.01±9.76</td>
</tr>
<tr>
<td>Number of diseased major epicardial coronary artery ≥2 (stenosis≥50%)</td>
<td>81(21.0%)</td>
<td>68(19.1%)</td>
</tr>
</tbody>
</table>

Medication

- Antiplatelet agents
- Nitrates
- Beta-blockers
- ACEI/ARB
- CCB
- Statins


with stable angina pectoris. The results suggest that measuring the RDW level may provide valuable information for one-year risk stratification of stable angina pectoris patients. We found a graded, independent association between the baseline RDW level and the risk of cardiac death, as well as the development of ACS, in a Chinese population of individuals with stable angina pectoris who were free of clinically evident heart failure or ACS at baseline. The results support the hypothesis of a linkage between abnormalities in the RDW and the prognosis of stable angina pectoris.

The RDW is a numerical measure of the variability in size of circulating erythrocytes (9). Its use is generally restricted to narrowing the differential diagnosis of anemia and other conditions of ineffective red cell production, increased red cell destruction and blood transfusion (10). However, none of these conditions were present in our study population and adjusting for multiple potential confounders attenuated but did not eliminate the association between higher RDW levels and adverse clinical outcomes.

Recently, population studies have identified the RDW to be a predictor of cardiac mortality (11). The RDW is included as a key element in a published mortality risk score (12). However, the mechanisms by which elevated values of RDW are associated with adverse outcomes of stable angina pectoris remain unknown, especially in Chinese individuals. It has been suggested that the RDW may reflect other known markers of prognosis in patients with heart failure (13, 14). The evidence that inflammation plays a pivotal...
role in the pathogenesis of most of cases of ACS led to the use of inflammatory mediators as markers of risk in patients with these syndromes (15). Inflammatory cytokines have been found to suppress the maturation of erythrocytes, allowing juvenile erythrocytes to enter into circulation thereby leading to an increase in heterogeneity of the size of these cells (16, 17). Furthermore, higher RDW values may reflect enhanced erythropoiesis resulting from elevated circulating levels of neurohumoral mediators (18). Whether stable angina pectoris is affected by the same pathogenetic mechanisms of chronic inflammatory and neurohumoral activation is unclear. We speculate that higher levels of RDW may reflect an underlying inflammatory state, associated with adverse clinical outcomes and impaired erythrocyte maturation. Inflammatory states are strongly related to ineffective erythropoiesis. Inflammatory cytokines desensitize bone marrow erythroid progenitors and inhibit RBC maturation (19, 20).

In the present study, the RDW was positively correlated with log (BNP) (r=0.230, p<0.001) and log (hs-CRP) (r= 0.147, p<0.001). In a large prospective study conducted by Lappé et al., a significant correlation was found between the RDW and the hs-CRP level (r=0.181; p<0.001) in patients with coronary artery disease (CAD) that remained significant following full adjustment for several confounding factors (21). Fukuta et al. (22) observed a significant correlation between the BNP level and the RDW in patients undergoing cardiac catheterization for CAD, suggesting the existence of a potential interplay between anosocytosis and neurohumoral mediators. In other clinical investigations, significant and positive associations have been found between the RDW and a variety of inflammatory markers (10, 23, 24). A variety of vasoconstrictive neurohormones including angiotensin II and norepinephrine have been found to directly enhance BNP secretion (22, 25). These aspects may explain why the RDW was found to be positively correlated with the levels of BNP and hs-CRP in our study. However, the correlation coefficients between the RDW and the levels of BNP and hs-CRP were both low and the time of blood collection may have affected these values. Therefore, in this study we were unable to identify the exact mechanisms underlying the association between higher RDW values and an increased incidence of adverse outcomes in patients with stable angina pectoris. Additional studies should be performed to determine the underlying factors that affect the RDW.

The present study is associated with several limitations. First, this was a post hoc observational analysis, and we therefore cannot rule out the possibility of residual confounding. However, the hypothesis that the RDW levels is associated with adverse outcomes was formulated before the analyses were conducted, reducing the risk of spurious conclusions. Second, we did not assess other outcomes in our analysis, such as malignant arrhythmia and acute or chronic heart failure which are important end points of coronary heart disease. Third, we did not measure the plasma levels of angiotensin II or norepinephrine in our patients. Last, we did not have data on changes in the RDW values during the one-year follow-up. The changes in the RDW values observed during a one-year course of stable angina pectoris may better predict more clinical outcomes.

In conclusion, in patients with stable angina pectoris, elevated RDW values predict an increased risk of one-year adverse outcomes. More studies are needed to address the underlying mechanisms and treatment. These findings are also notable given that the RDW is an easy, inexpensive and routinely reported test, whose assessment may allow for the acquisition of significant diagnostic and prognostic information in patients with cardiovascular disorders.

The authors state that they have no Conflict of Interest (COI).
References