Red Cell Distribution Width Can Predict the Significance of Angiographically Intermediate Coronary Lesions

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Abstract
Objective: In the present study, the association between red cell distribution width (RDW) with functional significance of intermediate coronary artery lesions was investigated. Materials and Methods: Two hundred and forty-six consecutive patients, 168 males and 78 females, who underwent fractional flow reserve (FFR) measurement for angiographically intermediate coronary stenosis (40–70% in quantitative coronary analysis) in the left anterior descending coronary artery were enrolled into the study. The functional significance of intermediate coronary artery lesions was determined by FFR measurement. An FFR value <0.75 was defined as functionally significant. Venous blood samples were taken within 48 h before the FFR measurement, and RDW levels were determined by a Coulter LH Series hematology analyzer. Logistic regression analysis was used to examine the association between functional significance in FFR measurement and other variables. Results: Of the 246 patients, 62 (25.2%) exhibited significant functional stenosis (FFR <0.75) in the FFR measurement. The mean RDW level was significantly higher in patients with significant stenosis (14.19 ± 0.73 vs. 13.69 ± 0.77, p < 0.001). In stepwise multivariate logistic regression analysis, RDW (OR = 2.489, 95% CI = 1.631–3.799, p < 0.001) and male gender (OR = 2.826, 95% CI = 1.347–5.928, p = 0.006) were independent predictors of significant functional stenosis. Conclusion: Increased RDW levels were associated with functional significance of angiographically intermediate coronary artery stenoses.

Introduction
Coronary angiography plays an essential role in the assessment of epicardial coronary artery lesions [1]. It is of great importance to determine the functional significance of angiographically intermediate coronary artery stenoses, because it is the most important factor regarding clinical outcome and is essential for revascularization decision [2, 3]. However, coronary angiography has limited accuracy in defining the functional significance of a coronary artery stenosis, and fractional flow reserve (FFR) has been widely used as an accurate and lesion-specific tool which indicates the functional significance of a particular lesion [4–6].

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Red cell distribution width (RDW) is a readily available part of routine complete blood cell counts and a relatively novel marker of inflammation and oxidative stress [7, 8]. Previous studies [9–11] showed that RDW is associated with numerous cardiovascular conditions. Increased RDW is a negative prognostic marker in patients with heart failure, stable coronary artery disease and ST elevation myocardial infarction. A relationship between RDW and myocardial ischemia had been shown in dobutamine stress echocardiography [12]. However, the relationship between RDW and functional significance of coronary artery lesions in FFR has not been investigated. Thus, the aim of this study was to investigate the relationship between RDW and the functional significance of angiographically intermediate coronary artery stenoses.

**Subjects and Methods**

A total of 314 consecutive patients who underwent FFR measurement for intermediate lesions (40–70% stenosis in quantitative coronary analysis) in the left anterior descending artery from January 2012 to June 2013 were enrolled in this study. Clinical, demographic and angiographic data of the patients were obtained from hospital records. Exclusion criteria were patients with previous myocardial infarction, history of heart failure, severe arrhythmia, anemia according to WHO criteria (hemoglobin value for males <13 g/dl, for females <12 g/dl) [13], blood transfusion in the last 6 months, acute infection, chronic kidney disease (creatinine clearance <60 ml/min), hemotological diseases, malignancy, chronic systemic disease and patients with critical lesions in other coronary arteries and tandem lesions. Based on the exclusion criteria, 68 patients were rejected; the remaining 246 patients formed our study population. Among the participants, 144 had hypertension, and 74 had diabetes mellitus. The study was approved by the Local Ethics Committee. Venous blood samples were taken within 48 h before the FFR measurement for biochemical and hematological measurements including complete blood count, serum creatinine and lipid profile. The RDW levels were determined by a Coulter LH Series hematology analyzer (Beckman Coulter Inc., Hialeah, Fla., USA).

**FFR Measurement**

After administration of an intra-arterial heparin bolus of 5,000 units, the coronary artery was engaged using a guiding catheter without side holes. Then, a 0.014-inch pressure monitoring guidewire (PrimeWire, Volcano, San Diego, Calif., USA) was calibrated and positioned distally to the stenosis. An intracoronary nitroglycerin bolus of 200 μg was given 2 min before FFR measurement to prevent vasospasm. Baseline distal intracoronary pressure was recorded, and intracoronary adenosine was administered to induce maximum hyperemia by successively increasing the adenosine dose until no further decrement in the FFR value was observed. FFR was calculated as the ratio of mean distal intracoronary pressure to the mean aortic pressure at the time of peak hyperemia. An FFR value <0.75 was defined as functionally significant.

**Statistical Analysis**

The SPSS statistical software (SPSS 17.0 for Windows, SPSS Inc., Chicago, Ill., USA) was used for data analysis. Quantitative data are presented as means ± standard deviation and categorical variables presented as percentages. The data were tested for normal distribution using the Kolmogorov-Smirnov test. Student’s t or Mann-Whitney U tests, as appropriate, were used to compare continuous variables. The χ² test was used to identify statistically significant differences for categorical variables. Logistic regression analysis was used to examine the association between functional significance in FFR measurement and other variables. Variables with a p value of <0.1 in univariate logistic regression analysis were included in a multivariate logistic regression model. A 2-tailed p < 0.05 was considered significant.

**Results**

The mean age of the 246 participants was 61.4 ± 10.9 years. Of the 246 patients, 62 (25.2%) exhibited significant functional stenosis, and 184 (74.8%) exhibited non-significant stenosis in the FFR measurement. The mean RDW was significantly higher in patients with significant stenosis (14.19 ± 0.73 vs. 13.69 ± 0.77, p < 0.001). Other baseline variables, including use of cardiovascular medicine, were similar in both patients with significant and nonsignificant stenosis (table 1). In stepwise multivariate logistic regression analysis, RDW and male gender were independently associated with significant functional stenosis in the FFR measurement (table 2). The receiver operating characteristic curve analysis showed that for the RDW at a cutoff point of 13.85% sensitivity and specificity were 69.4 and 65.8%, respectively, in detecting significant functional stenosis in the FFR measurement (fig. 1).

**Discussion**

In this study, RDW levels were independently associated with functionally significant lesions using FFR measurements of angiographically intermediate coronary stenosis, and male gender was the other independent predictor of functional significance.

Functionally significant stenoses cause inducible ischemia and are associated with worse outcomes [14]. In contrast, if a stenosis has no functional significance, a favorable outcome can be expected with medical treatment [15]. FFR is linearly related to maximum blood flow to the myocardial distribution of the respective artery, and it can indicate the functional significance of a particular lesion irrespective of the factors like patient, artery and
### Table 1. Clinical, laboratory and angiographic characteristics of the patients

|                          | Nonsignificant stenosis (n = 184) | Significant stenosis (n = 62) | All (n = 246) | p value |
|--------------------------|----------------------------------|-------------------------------|---------------|---------|
| Age, years               | 61.0 ± 10.3                      | 62.77 ± 12.4                  | 61.4 ± 10.9   | 0.278   |
| Gender                   |                                  |                               |               |         |
| Male                     | 120 (65.3)                       | 48 (77.5)                     | 168 (68.3)    | 0.074   |
| Female                   | 64 (34.7)                        | 14 (22.5)                     | 78 (31.7)     |         |
| Hypertension             | 110 (59.7)                       | 34 (54.8)                     | 144 (58.5)    | 0.494   |
| Diabetes mellitus        | 54 (29.3)                        | 20 (32.2)                     | 74 (30.1)     | 0.666   |
| Smoking                  | 68 (36.9)                        | 30 (48.3)                     | 98 (39.8)     | 0.112   |
| Hemoglobin, g/dl         | 14.13 ± 1.67                     | 13.84 ± 1.39                  | 14.03 ± 1.60  | 0.218   |
| MCV, fl                  | 88.2 ± 4.4                       | 88.8 ± 5.0                    | 88.3 ± 4.6    | 0.415   |
| RDW, %                   | 13.69 ± 0.77                     | 14.19 ± 0.73                  | 13.82 ± 0.79  | <0.001  |
| WBC                      | 8,313 ± 2,188                    | 8,778 ± 2,134                 | 8,430 ± 2,179 | 0.147   |
| Platelets (×1,000)       | 274.3 ± 74.3                     | 290.0 ± 91.4                  | 278.3 ± 79.0  | 0.176   |
| Creatinine, mg/dl        | 1.09 ± 1.29                      | 1.11 ± 1.44                   | 1.10 ± 1.35   | 0.123   |
| Total cholesterol, mg/dl | 187.4 ± 42.4                     | 189.1 ± 46.9                  | 187.8 ± 43.5  | 0.780   |
| LDL-C, mg/dl             | 115.4 ± 38.5                     | 117.6 ± 38.9                  | 116.0 ± 38.6  | 0.693   |
| HDL-C, mg/dl             | 40.7 ± 11.3                      | 42.6 ± 9.3                    | 41.2 ± 10.9   | 0.245   |
| Triglyceride, mg/dl      | 163.1 ± 92.6                     | 149.0 ± 81.6                  | 157.5 ± 90.3  | 0.095   |
| Statin                   | 39 (21.2)                        | 12 (19.4)                     | 51 (20.7)     | 0.757   |
| ACE-I                    | 54 (29.3)                        | 16 (25.8)                     | 70 (28.5)     | 0.593   |
| β-Blocker                | 24 (13.0)                        | 10 (16.1)                     | 34 (13.8)     | 0.543   |
| Calcium channel blocker  | 38 (20.7)                        | 12 (19.4)                     | 50 (20.3)     | 0.826   |
| Aspirin                  | 59 (32.1)                        | 22 (35.5)                     | 81 (32.9)     | 0.620   |
| Diameter of stenosis, %  | 55.05 ± 9.69                     | 56.77 ± 10.2                  | 55.49 ± 9.83  | 0.234   |

Results are presented as means ± SD or numbers with percentages in parentheses. MCV = Mean corpuscular volume; WBC = White blood cell; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ACE-I = angiotensin-converting enzyme inhibitor.

### Table 2. Factors predicting functional significance in logistic regression analysis

| Variables                  | Univariable |     | Multivariable |     |
|----------------------------|-------------|-----|---------------|-----|
|                            | OR          | p value | OR          | p value |
| Age                        | 1.015 (0.988 – 1.042) | 0.278 | – | – |
| Male gender                | 1.829 (0.937 – 3.567) | 0.077 | 2.826 (1.347 – 5.928) | 0.006 |
| Hypertension               | 1.224 (0.685 – 2.188) | 0.495 | – | – |
| Diabetes mellitus          | 1.146 (0.617 – 2.131) | 0.666 | – | – |
| Percent diameter stenosis  | 1.018 (0.988 – 1.049) | 0.234 | – | – |
| Hemoglobin                 | 0.964 (0.909 – 1.022) | 0.218 | – | – |
| WBC                        | 1.000 (1.000 – 1.000) | 0.147 | – | – |
| MCV                        | 1.026 (0.964 – 1.093) | 0.414 | – | – |
| RDW                        | 2.218 (1.498 – 3.283) | <0.001 | 2.489 (1.631 – 3.799) | <0.001 |
| Platelets                  | 1.000 (1.000 – 1.000) | 0.177 | – | – |
| Creatinine                 | 1.379 (0.445 – 4.273) | 0.124 | – | – |
| LDL-C                      | 1.002 (0.994 – 1.009) | 0.692 | – | – |
| HDL-C                      | 1.016 (0.989 – 1.042) | 0.245 | – | – |
| Triglyceride               | 0.997 (0.993 – 1.001) | 0.098 | 0.997 (0.994 – 1.001) | 0.164 |

Figures in parentheses indicate 95% CI. WBC = White blood cell; MCV = mean corpuscular volume; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol.
blood pressure [16]. FFR is established as the gold standard for the assessment of the significance of a coronary stenosis [16, 17]. Thus, we chose FFR to determine the functional significance of coronary lesions and its relationship with the RDW level.

The mechanism of the increased RDW in functionally significant coronary artery stenosis is not clear. It is possible that ischemia caused by functionally significant lesions is responsible for increased inflammation and oxidative stress, and, thus, leads to increased RDW. It is known that inflammation impairs iron metabolism and inhibits the response to erythropoietin [18]. Tumor necrosis factor α and interleukin 6 are responsible for the attenuation of the activity of erythropoietin and the production of ineffective red blood cells (RBCs) [7]. Inflammation may also lead to an increase in RDW by disturbing the red cell membrane and inducing changes in RBC maturation [18]. Oxidative stress causes shortened RBC survival by increasing the fragility of RBCs [19] and decreasing the rate of erythroid maturation [20]. The result of the shortened RBC survival is increased RDW. In addition, increased RDW was found to be associated with impaired RBC deformability and increased blood viscosity, and such hemorheological alterations may cause slow coronary flow and contribute to the myocardial ischemia [21, 22].

Male gender was the other predictor of functional significance in our study. Previously, Fineschi et al. [23] demonstrated that despite similar clinical and angiographic characteristics, male patients have significantly lower FFR values in response to adenosine. However, the mechanism of this observation remains to be established.

Previous studies revealed the value of RDW in various cardiovascular settings. Higher RDW levels predicted stent restenosis, contrast-induced nephropathy and increased mortality in patients undergoing percutaneous coronary intervention [11, 24, 25]. Furthermore, increased RDW is associated with poor clinical outcomes, mortality and recurrent myocardial infarction in patients with acute coronary syndrome [25–28]. Our study is another one to show the possible use of RDW in cardiology practice. Since patients with functionally significant coronary stenosis have relatively worse outcomes [14], increased RDW levels may also indicate poor clinical outcomes in our study population. However, further studies with long-term follow-up are required to show such an association.

The main limitation of this study was its single-center and retrospective design. Therefore it is not possible to distinguish between association and causal relationship when interpreting its results. Another limitation of the study was that serum vitamin B12, folate and iron levels which might influence RDW were not measured. Oxidative stress and inflammation were not assessed by different markers since RDW has been established as an independent marker of inflammation and oxidative stress.

**Conclusion**

The results of the current study showed that RDW were independently associated with functional significance of intermediate coronary artery stenoses in FFR measurements. Further studies are needed to elucidate the exact role of RDW in predicting functionally significant coronary artery disease.

**Disclosure Statement**

There are no conflicts of interest.

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