Increased red cell distribution width level is associated with absence of coronary collateral vessels in patients with acute coronary syndromes

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Objectives: Several studies have evaluated a relationship between increased red cell distribution width (RDW) and morbidity and mortality of acute coronary syndrome (ACS). In this study, we aimed to investigate the association of serum RDW levels and development of coronary collateral vessel (CCV) in patients with ACS.

Study design: We evaluated 226 patients with ACS in this prospective and cross-sectional study. Traditional laboratory and clinical parameters and serum RDW levels were measured on admission. All patients underwent coronary angiography on the first day after admission and patients with >80% stenosis were included in the study. The CCV was graded according to the Rentrop scoring system, and a Rentrop grade 0 was accepted as no CCV development (Group 1), while Rentrop grades 1-2-3 were accepted as presence of CCV development (Group 2).

Results: Only levels of RDW were significantly higher in Group 1 than in Group 2 (Group 1 RDW 14.6±1.9, Group 2 RDW 14.1±1.4, p=0.02). The predictive value of serum RDW level for absence of collaterals (sensitivity of 58% and specificity of 54%, area under the receiver operating characteristic (ROC) curve = 0.573) was 13.90.

Conclusion: We found that high levels of RDW were associated with absence of CCV in patients with ACS.

Red cell distribution width (RDW) is a laboratory measure of the variability in erythrocyte volume and is a readily available component of the routine complete blood count. Recent studies have shown that high RDW levels were associated with adverse outcomes in patients with ST elevation myocardial
infarction (STEMI) and heart failure. High levels of RDW are also associated with increased mortality in patients with coronary artery disease (CAD) and patients undergoing percutaneous coronary intervention. Furthermore, a relationship between RDW and the severity and complexity of CAD was shown in previous studies. In spite of these associations, the mechanisms underlying elevated RDW are unclear in these patient groups. Inflammation and neurohumoral mediators may stimulate changes in the red cell membrane, leading to increased RDW.

Coronary collateral vessels (CCVs) can provide a perfusion reserve in case of increased myocardial oxygen demand. Coronary collaterals can limit the myocardial ischemia and can protect the viable myocardium in patients with acute coronary syndrome (ACS). The absence of CCVs is correlated with worse clinical outcomes in patients with ACS. The absence of CCV in patients with ACS who had high levels of serum RDW may explain the relation between elevated serum RDW and worse clinical outcomes in patients with ACS.

The complex mechanisms in the development of CCV are not well understood. Some mediators (such as C-reactive protein, uric acid, and circulating endothelial progenitor cells) were investigated to explain the development of CCV, but there is not yet conclusive evidence. Moreover, as serum RDW predicted the risk of CAD and cardiac mortality, it may also be interesting to examine whether serum RDW predicts the presence of coronary collaterals (especially via oxidative stress), one of the major predictors of mortality in patients with ACS. In this study, we aimed to investigate the association of serum RDW levels and development of CCV in patients with ACS.

**PATIENTS AND METHODS**

**Patients**

This was a prospective and cross-sectional study. A total of 370 consecutive patients who had admitted to the hospital between February 2010 and May 2011 with ACS defined as either unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) and undergone coronary angiography were examined. UA was diagnosed according to the following criteria: typical chest pain and/or electrocardiographic changes indicating myocardial ischemia with negative cardiac enzymes. NSTEMI diagnosis was based on elevated cardiac enzymes with typical chest pain and/or electrocardiographic changes suggestive of myocardial ischemia. Typical chest pain was evaluated as follows: more than 20 minutes (min) in duration, new-onset angina, and an increase in its frequency and duration or severity. Each subject was questioned about major risk factors for CAD and development of CCV including diabetes (defined as a fasting blood glucose level >110 mg/dl or using antidiabetic drugs), hypertension (defined as blood pressure of 140/90 mmHg or more or taking antihypertensive medications), chronic obstructive pulmonary disease, and current smoking and alcohol status.

Patients with histories of coronary intervention/ coronary artery bypass, cardiac failure, renal disease (or serum creatinine level >1.5 mg/dl), or inflammatory rheumatic disease; anemia; clinical evidence of active infection; active cancer; hematological proliferative diseases; active or chronic inflammatory or autoimmune diseases; pregnancy; recent blood transfusion; a history of chronic obstructive pulmonary disease; or severe arrhythmia were excluded. The patients with less than 80% stenosis in the coronary angiography were also excluded from the study. Finally, 226 patients (UA, 93 patients and NSTEMI, 133 patients) were included in the study.

Anemia was defined as hemoglobin levels lower than 13 g/dl in men and 12 g/dl in women, in accordance with the World Health Organization criteria.

Informed consent was obtained from all patients. The study was approved by our local ethical committee. All demographic and clinical data were collected prospectively.

**Laboratory analysis**

In all cases, blood samples were drawn at admission before starting any medication and were collected in tripotassium EDTA tubes. All measurements were performed 30 min after blood collection by an automatic blood counter (A Sysmex XE-2100, Symex, Kobe, Japan).
Coronary angiography
Quantitative coronary angiography was performed by the Judkins technique via the right femoral artery by two experienced interventional cardiologists who had no knowledge of the patients’ clinical information. Coronary arteries were imaged by utilizing right and left anterior oblique views with cranial and caudal positions. Injection of contrast medium (Iopromide, Ultravist-370; Schering AG, Berlin, Germany) was carried out by an automatic injector at a speed of 3-4 ml/seconds (sec) for the left coronary artery and 2-3 ml/sec for the right coronary artery. Arteriographies were recorded at a speed of 25 frames/sec. Coronary vessel disease was described as degree of diameter stenosis of 80% or greater in at least one coronary artery. Collateral circulation was graded according to the Rentrop classification. The collateral circulation was based on the injection that best opacified the occluded vessel: 0= no visible filling of any collateral vessels, 1= filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2= partial filling of the epicardial segment by collateral vessels, and 3= complete filling of the epicardial segment by collateral vessels. Rentrop grade 0 was accepted as no development of CCV (Group 1) and Rentrop grade ≥1 was accepted as presence of CCV (Group 2).

Statistical analysis
All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v 16.0 for Windows (version 16.0, SPSS, Chicago, IL, USA). Quantitative variables were expressed as mean value ± SD for continuous variables and median and minimum-maximum levels for categorical variables/string variables. Comparison of continuous values between two groups was performed by means of independent-samples t test. Comparison of categorical variables/string variables between two groups was performed by Mann-Whitney U-test. Categorical variables were compared by the chi-squared test. Pearson test was used for correlation parametric variables and Spearman test for non-parametric variables. Two-tailed $p$ value <0.05 was considered statistically significant. In the univariate analysis, only levels of RDW were associated with absence of CCV. Multiple logistic regression analysis was not performed. Receiver operating characteristics (ROC) analysis was performed. The best cutoff value of RDW was determined, and the sensitivity and specificity at that point were determined.

RESULTS
The baseline demographic and clinical patient characteristics are presented in Table 1. There was no significant difference in the presence of diabetes mellitus, hypertension, smoking, gender, age, and systolic-diastolic blood pressure between Groups 1 and 2. Only levels of RDW were significantly higher in Group 1 than in Group 2 (Group 1 RDW 14.6±1.9, Group 2 RDW 14.1±1.4, $p=0.02$). Other laboratory parameters were similar between the two groups (Table 2).

### Table 1. Relation between presence of coronary collaterals and baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>All (n=226)</th>
<th>Group 1 (n=110)</th>
<th>Group 2 (n=116)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Mean±SD</td>
<td>n</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±11</td>
<td>62±11</td>
<td>61±11</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>171</td>
<td>75.7</td>
<td>82</td>
<td>74.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>127</td>
<td>56.2</td>
<td>85</td>
<td>59.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39</td>
<td>17.3</td>
<td>17</td>
<td>15.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31</td>
<td>13.7</td>
<td>11</td>
<td>10.0</td>
</tr>
<tr>
<td>USAP</td>
<td>93</td>
<td>41.2</td>
<td>50</td>
<td>45.0</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>133</td>
<td>58.8</td>
<td>60</td>
<td>54.5</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>110.2±16.0</td>
<td>115.6±14.5</td>
<td>114.2±17.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70.1±11.9</td>
<td>72.6±12.0</td>
<td>70.7±11.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

USAP: Unstable angina pectoris; NSTEMI: Non-ST elevation myocardial infarction; BP: Blood pressure.
The predictive value of serum RDW level for absence of collaterals (sensitivity of 58% and specificity of 54%, area under the ROC curve = 0.573) was 13.90 (Fig. 1).

**DISCUSSION**

To our knowledge, this is the first study to evaluate the relationship between RDW and the development of coronary collateral circulation. Our observations suggest that elevated levels of RDW are associated with absence of CCVs in patients with ACS.

Well-developed CCVs can limit the myocardial ischemia, may minimize the infarct size and can protect the viable myocardium in patients with ACS. The absence of CCV is correlated with bad clinical outcomes in patients with ACS. Resting distal coronary pressure consistently falls as stenosis severity exceeds 70%. Myocardial ischemia, growth factors and shear stress are factors that likely contribute to initiating and remodeling for collateral development during the tissue hypoxia. The severity of CAD and the duration of myocardial ischemic symptoms were described as influencing the development of coronary collaterals.

Vascular growth is usually categorized as angiogenesis (new capillaries from pre-existing ones) or arteriogenesis (the *in situ* development of vessels from angioblasts). The underlying mechanisms of this collateral growth depend on the expression of numerous growth factors and signaling cascades. Reactive oxygen species (ROS), which are free radicals, contain lots of molecules produced in all aerobic cells including molecular oxygen and its derivatives. In pa-
Patients with acute coronary syndromes and increased red cell distribution width level

Red cell distribution width is a marker of the variability in erythrocyte volume and is a routinely available component of the complete blood count. Elevated RDW reflects the heterogeneity of cell sizes in the peripheral blood smear. Elevated RDW levels can be seen in conditions of ineffective red cell production (such as iron deficiency, B12 or folate deficiency and hemoglobinopathies), increased red cell destruction (such as hemolysis), and with blood transfusion.

The underlying mechanism by which high levels of RDW are associated with development of CCVs in ACS is unclear. Inflammation has an important role in the atherosclerotic process and coronary collateral circulation. Inflammatory cytokines, which are activated in ACS, have been found to suppress the erythrocyte maturation, so juvenile erythrocytes enter into the circulation. Also, elevated levels of neurohumoral mediators stimulate erythropoiesis; for example, angiotensin II may affect the erythroid progenitor cells with direct stimulation. In addition, levels of erythropoietin increase independent of hemoglobin levels, and adrenergic activation may act on bone marrow response in patients with ACS. There is a substantial genetic contribution to red cell size in the general population. The variability in circulating red cell sizes may increase with these mechanisms. Investigators have shown a relationship between elevated levels of RDW and both generalized inflammation and oxidative stress, which are proposed as key mechanisms of atherosclerosis and absence of collaterals.

Several studies have evaluated the relationship between increased RDW and morbidity and mortality of CAD. Investigators showed that an increased RDW was independently associated with in-hospital and long-term all-cause mortality and coronary events in STEMI and NSTEMI in an unselected population of male patients referred for coronary angiography. Also, in other studies, a high admission RDW was independently associated with worse reperfusion and increased risk of in-hospital and long-term cardiovascular mortality in patients with STEMI undergoing primary percutaneous intervention. In a study of 7556 adult participants (divided into 3 categories according to their 10-year Framingham risk of hard CAD events, as <10%, 10-20%, >20%), it was found that a higher RDW might be a powerful independent predictor of future coronary heart disease risk. Isik et al. demonstrated that RDW was independently associated with the presence of CAD and coronary complexity of CAD as assessed by the SYNTAX score.

Only hemoglobin levels were measured in this study and not other factors such as levels of iron, vitamin B12, folate, and mean corpuscular volume. However, we did not include the patients with anemia in our study. We believe that this makes it highly unlikely that the predictive value of RDW was related to iron deficiency. Furthermore, the incidence of clinically significant vitamin B12 and folate deficiency is low in a modern population. In a study of 15852 adult participants, RDW was found to be an independent predictor of mortality, and the investigators concluded that the relationship between RDW and mortality was not confounded by anemia-related deficiencies such as vitamin B12, folate or iron.

In conclusion, we found that high levels of RDW were associated with absence of CCVs in patients with ACS. We also think that RDW is a widely available marker with no additional costs, in contrast to other novel markers of cardiovascular risk.

Limitations

There are several limitations to our study. We did not evaluate other novel risk factors for STEMI in young patients, such as fibrinogen, CD 40 ligand, factor V Leiden, protein C, and antithrombin III, and could not evaluate the medical history of patients. Only hemoglobin levels were measured in this study and not other factors such as levels of iron, ferritin, vitamin B12, and folate. We also did not evaluate the duration of angina or degrees of exercise capacity, which are important for development of CCVs.
Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Acute coronary syndrome; biological markers; coronary circulation; erythrocyte indices; red cell distribution width.

Anahtar sözcükler: Akut koroner sendrom; biyolojik belirteç; koroner dolaşım; eritrosit indeksi; eritrosit dağılım genişliği.