The Relationship Between Coronary Collateral Circulation and Red Blood Cell Distribution Width

Koroner Kollateral Akım ve Kırmızı Küre Dağılım Genişliği Arasındaki İlişki

Hasan KADI, MD,[a]
Köksal CEYHAN, MD,[a]
Fatih KOÇ, MD,[a]
Ataç ÇELİK, MD,[a]
Orhan ÖNALAN, MD[a]

Department of Cardiology,
Gaziosmanpaşa University
Faculty of Medicine, Tokat

Geliş Tarihi/*Received:* 07.05.2010
Kabul Tarihi/*Accepted:* 24.01.2011

Yazışma Adresi/*Correspondence:*
Hasan KADI, MD
Gaziosmanpaşa University
Faculty of Medicine,
Department of Cardiology, Tokat,
TÜRKİYE/TURKEY
drhkadi@hotmail.com

ABSTRACT Objective: The red blood cell distribution width (RDW) is the quantitative measurement of the size variability of red blood cells. It has been reported that high levels of RDW may serve as a predictor of mortality and morbidity in patients with heart disease. Coronary collateral circulation (CCC) is an alternative source to provide blood to the ischemic area in patients with coronary artery disease. Many studies have shown that CCC has positive effects on left ventricular function. In this study, we aimed to investigate the relationship between CCC and RDW. **Material and Methods:** We assessed 231 patients who have at least one occluded major coronary artery. CCC was graded according to Rentrop classification. Rentrop 0 and 1 were classified as insufficient CCC; Rentrop 2 and 3 were classified as sufficient CCC. We collected fasting blood samples and measured RDW, N-terminal pro B-type natriuretic peptide (NT-proBNP) and high sensitive C-reactive protein (hs-CRP) before the coronary angiography. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method. **Results:** RDW values (%) were found higher in patients with the insufficient CCC compared to the sufficient CCC [14.9 (12.3-19.6) versus 13.2 (11.3-18.3), p< 0.001]. NT-proBNP (pg/l) and hs-CRP (mg/dl) values were found to be much higher in the insufficient CCC group as compared to the sufficient group [1319 (138-9753) vs 960 (25-7785), 6.9 (3.1-15.5), 3.6 (2.2-14.9), p= 0.012, p= 0.002, respectively]. LVEF (%) was found to be low in the insufficient CCC group compared to sufficient CCC group [45 (30-60) vs 50 (30-60), p< 0.001]. **Conclusion:** We found higher RDW levels in patients with insufficient CCC than in patients with sufficient CCC. We hypothesize that high RDW levels in patients with insufficient CCC may be related to both increased neurohormonal activity and increased inflammation.

Key Words: Collateral circulation; erythrocytes; coronary artery disease

ÖZET Amaç: Kırmızı küre dağılım genişliği (RDW) kırmızı kan hücrelerinin büyüklüklerindeki değişkenliğin nümerik bir ölçümüdür. Yüksek RDW düzeylerinin kalp hastalıklı hastalarda mortalite ve morbiditenin bir öngördürücüsü olduğu bildirilmiştir. Koroner kollateral dolaşım (CCC) koroner arter hastalıklı hastalarda iskemik olan bölgeye kan sunumunun alternatif kaynağıdır. Koroner kollateral dolaşımın sol ventrikül fonksiyonu üzerine olumlu etkisinin olduğunu gösteren birçok çalışma vardır. Bu çalışmadaki amacımız CCC ve RDW arasındaki ilişkiyi araştırmaktır. **Gereç ve Yöntemler:** En az bir major koroner arteri tam tıkalı olan 231 hastayı değerlendirdik. Kollateral akım derecelendirilmesi Rentrop sınıflamasına göre yapıldı. Rentrop 0 ve 1 yetersiz, Rentrop 2 ve 3 yeterli CCC olarak değerlendirildi. Koroner anjiyografi öncesi alınan açlık kan örneğinden RDW, N-terminal pro B-tipi natriüretik peptit (NT-pro BNP), yüksek sensitif C-reaktif protein (hs-CRP) ölçümleri yapıldı. Sol ventrikül ejeksiyon fraksiyonu (LVEF) modifiye Simpson metodu ile ölçüldü. **Bulgular:** Yetersiz CCC grubunda RDW (%) değeri-ortanca (minimum-maksimum)-yeterli CCC grubundakinden daha yüksek bulundu [14.9 (12.3-19.6) ve 13.2 (11.3-18.3), p< 0.001)]. Kan NT-pro BNP (pg/ml) ve hs-CRP (mg/dl) düzeyleri-ortanca (minimum-maksimum)- yetersiz kollateral grubunda daha yüksek idi [sırasıyla, 1319 (138-9753), 960 (25-7785), 6.9 (3.1-15.5), 3.6 (2.2-14.9), p=0.012, p=0.002]. Yetersiz kollateral grubunda LVEF (%) yeterli kollateral grubundakinden daha düşük bulundu [45 (30-60, 50 (30-60), p< 0.001)]. **Sonuç:** Yetersiz CCC grubunda RDW düzeylerini yeterli CCC grubundakinden yüksek bulduk. Yetersiz CCC grubundaki RDW yüksekliği artmış nörohormonal aktivite ve artmış inflamatuvar aktivite ile ilişkili olabilir.

Anahtar Kelimeler: Kollateral dolaşım; eritrositler; koroner arter hastalığı

Turkiye Klinikleri J Cardiovasc Sci 2011;23(1):23-8

The red blood cell distribution width (RDW) is the quantitative measurement of the size variability of red blood cells and is reported as a part of routine whole blood counting. It has been noted that the values of high RDW serve as a strong indicator for heart failure related mortality and morbidity.[1] In one particular study, a relationship between high RDW values and cardiovascular incidents, myocardial infarction, and subsequent death in the patients without symptomatic heart failure was observed.[2] A close relationship between increased left ventricular filling pressure and increased RDW levels were determined by echocardiogram in patients with acute heart failure.[3] It had been revealed that RDW is independent predictor for all cause-mortality in patients with coronary artery disease and it can be used as independent prognostic factor I these patients.[4] In another study, it was shown that RDW is an independent and strong marker for mortality in the patients where percutaneous coronary interventions were performed.[5] In the normal human heart, there are many collateral vessels binding major coronary arteries to each other.[6] The collateral channels of normal subjects and patients with mild coronary artery disease cannot be seen in a coronary angiogram due to their smallness and minimal current capacity. In order to see these small channels, the coronary artery needs to be occluded 99% or 100%.[7] Further, it has been well established that coronary collateral circulation (CCC) serves as an alternative source for providing blood to the ischemic area in patients with coronary artery disease. It has been shown that sufficient collateral flow limits the infarct-related area,[8] decreases both the frequency of cardiogenic shock after myocardial infarction[9] and the development of a left ventricular aneurysm,[10,11] protects the left ventricular function and maintains the ejection fraction.[12] We did not find any study in the literature which demonstrates a relationship between CCC and RDW. In this study, we aim to elucidate the relationship between CCC and RDW.

MATERIAL AND METHODS

PATIENTS

Patients who underwent coronary angiography between the January 2008 and January 2010 were evaluated to be in the study. All study participants had at least one angiographically occluded major coronary artery. Demographics, clinic and laboratory findings of the patients were recorded. We did not include the patients in the groups shown below:

1. Patients diagnosed with acute coronary within one month of the study.

2. Patients who had previously received a percutaneous coronary intervention or coronary artery surgery.

3. Patients who had been diagnosed with any systemic disease.

4. Patients who had been diagnosed with acute or chronic kidney failure.

5. Patients who had been diagnosed with class III-IV of NYHA functional capacity.

6. Patients who had been diagnosed with cancer, anemia, who had a blood transfusion in last 3 months or were pregnant.

7. Patients who had been diagnosed with severe valve narrowing and failure.

The study protocol was approved by institutional ethic committee

ANGIOGRAPHIC EVALUATION OF CORONARY COLLATERAL CIRCULATION

Coronary angiography was performed for all patients using the Judkins technique. Evaluation of collateral flow and examination of angiographies were performed by two experienced cardiologists without knowledge of clinical information or laboratory data of the patients. If there was an inconsistency between the two cardiologists, angiograms were evaluated by another cardiologist and a consensus was reached. Significant narrowing is described as when narrowing in diameter is over 50% in any major coronary artery. To classify collateral circulation we used Rentrop classification.[13]

Grades of collateral filling were classified as the following: 0= no filling; 1= filling of side branches via collateral channels without visualization of the epicardial segment; 2= partial filling of the epicardial major coronary via collateral chan-

nels; 3= complete filling of the epicardial major coronary of the artery. The vessel which had the highest Rentrop grade with collaterals was selected for analysis when there was more than one occluded vessel. In the case where there was more than one collateral vessel to the same blocked vessel then the highest Rentrop grade was used. Thus, Rentrop grades of 0 and 1 indicate insufficient collateral circulation while 2 and 3 indicate sufficient collateral circulation.[14] Echocardiographic left ventricular ejection fraction (LVEF) of patients was calculated between 1 to 7 days before the coronary angiography using the modified Simpson method.

BIOCHEMICAL PARAMETERS

RDW values were measured from fasting venous blood samples drawn before coronary angiography using a Pentra DX 120 analyzer (ABX, France). In our laboratory, the reference range of RDW is 11-16%. Plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) measurements and high sensitive C-reactive protein (hs-CRP) measurements were made 1 to 7 days before coronary angiography by electrochemiluminescence immunoassay method and immunonephelometry respectively.

STATISTICAL ANALYSIS

SPSS for Windows 15.0 (SPSS Inc. Chicago, Illinois, USA), a statistical packet program, was used for statistical analysis. Normal distributed continuous data were expressed as the mean ± standard deviation (SD); non-normal distributed continuous variables were presented as the median (minimum-maximum). Categorical data were expressed as numbers with percentages. Differences between the sufficient and the insufficient collateral groups were analyzed by using the Student's t-test for normally distributed continuous variables and Mann-Whitney U test for non-normally distributed continuous variables. Categorical data were compared by using the Chi-square test. RDW, NT-proBNP, LVEF and hs-CRP values were given as median (minimum-maximum). It was accepted as statistically significant when the p-value is under 0.05.

RESULTS

In total, we examined 2100 coronary angiograms performed between January 2008 and January 2009. We included 231 patients that fit our criteria in the study. We found 21 patients with Rentrop 0 CCC, 66 patients Rentrop 1 CCC, 58 patients Rentrop 2 CCC and 86 patients Rentrop 3 CCC. Thus, 87 patients were part of the insufficient CCC group and 144 patients the sufficient CCC group. The average age (mean ± SD) for the insufficient CCC group was 62.8 ± 9.4 years and for the sufficient CCC group, 61.7 ± 10.2 years. There was no significant difference between these two groups regarding to age, sex, hypertension, diabetes mellitus, dislipidemia, smoking, body mass index, hemoglobin values, hematocrit values, leukocytes numbers, localization of total occluded coronary artery and the number of diseased vessels. Demographics, clinic and laboratory findings for both groups were shown in Table 1 and coronary angiographic findings were shown in Table 2. RDW values (%) were 14.9 (12.3-19.6) in the insufficient CCC group and 13.2 (11.3-18.3) in the sufficient CCC group (Figure 1). NT-proBNP values (pg/l) were found to be 1319 (138-9753) in the insufficient CCC group and 960 (25-7785) in the sufficient CCC group (p=0.012) (Figure 2). Plasma hs-CRP values (mg/dl) were 6.9 (3.1-15.5) in the insufficient CCC group and 3.6 (2.2-14.9) units in the sufficient CCC group (p= 0.002) (Figure 3). LVEF (%) was found to be 45 (30-60) in the insufficient group and 50 (30-60) in the sufficient group (p< 0.001) (Figure 4).

DISCUSSION

RDW is a quantitative measurement of variability size of erythrocytes in circulating blood and is routinely reported as a part of a whole blood count. The major finding of our study is that RDW levels are higher in patients with insufficient CCC than in patients with sufficient CCC. Increased RDW is indicative of the production of immature erythrocytes in bone marrow. Notably, an elevated RDW level is commonly seen patients who lack folic acid, vitamin B12, and have received blood transfusions.[15] Moreover, severe blood loss, hemoglo-

TABLO 1: Baseline characteristics of patients in the insufficient collateral group and the sufficient collateral groups.

	Insufficient collateral group	Sufficient collateral group	P value
Age, years (mean ± SD)	62.8 ± 9.4	61.8 ± 10.2	0.442
Male, n (%)	62 (71.3)	102 (70.8)	0.944
Hypertension, n (%)	51 (58,6)	79 (54.9)	0.578
Dislipidemia, n (%)	46 (52.9)	77 (53.5)	0.930
Diabetes, n (%)	32 (36.8)	44 (30.6)	0.330
Smoking, n (%)	35 (40.2)	61 (42.4)	0.751
Previous MI, n (%)	60 (69.8)	84 (58.3)	0.107
Body mass index (kg/m2)	26 ± 3	27 ± 4	0.211
NT-proBNP (pg/l), median (min-max)	1319 (138-9753)	960 (25-7785)	0.012
hs-CRP (mg/dl), median (min-max)	6.9 (3.1-15.5)	3.6 (2.2-14.9)	0.002
LVEF (%), median (min-max)	45 (30-60)	50(30-60)	<0.001
RDW (%), median (min-max)	14.9 (12.3-19.6)	13.2 (11.3-18.3)	<0.001
Plt (count/mm3x1000) (mean ± SD)	257 ± 57	253 ± 56	0.566
Leukocyte (count/mm3) (mean ± SD)	7319 ± 1562	7049 ± 1482	0.186
Hemoglobin (gr/dl) (mean ± SD)	13.95 ± 0.9	13.96 ± 0.9	0.932
Hematocrit (%), (mean ± SD)	42 ± 3.3	42 ± 3.3	0.755

MI: Myocardial infarction, NT-proBNP: N terminal pro B-type natriuretic peptide, hs-CRP: High sensitive C-reactive protein,
LVEF: Left ventricular ejection fraction, RDW: Red cell distribution width, plt: platelet, min: Minimum, max: Maximum
NT-proBNP available in 130 patients, hs-CRP available in 120 patients.

TABLO 2: Coronary angiographic characteristics of patients in the insufficient collateral group and the sufficient collateral groups

	Insufficient collateral group	Sufficient collateral group	p value
Occluded LAD, n (%)	41 (47.1)	64 (44.4)	0.693
Occluded RCA, n (%)	35 (40.2)	75 (52.1)	0.081
Occluded CX, n (%)	25 (28.7)	38 (26.4)	0.699
1-vessel disease, n (%)	42 (48)	62 (43)	0.441
2-vessels disease, n (%)	20 (23)	44 (31)	0.214
3-vessels disease, n (%)	22 (25)	32 (22)	0.595

LAD: Left anterior descending artery, RCA: Right coronary artery, CX: Circumflex artery.

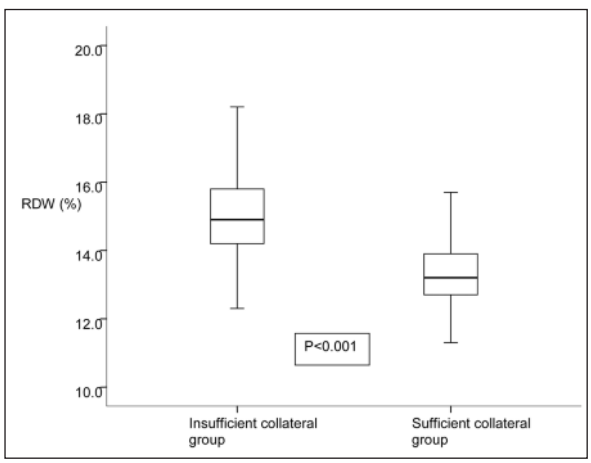

FIGURE 1: Red cell distribution width values in the insufficient collateral group and the sufficient collateral groups.
RDW: Red cell distribution width.

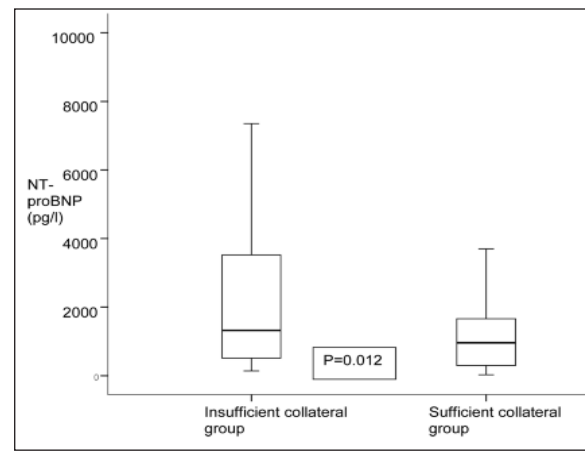

FIGURE 2: N-terminal pro B-type natriuretic peptide levels in the insufficient collateral group and the sufficient collateral groups.
NT-proBNP: N terminal pro B-type natriuretic peptide.

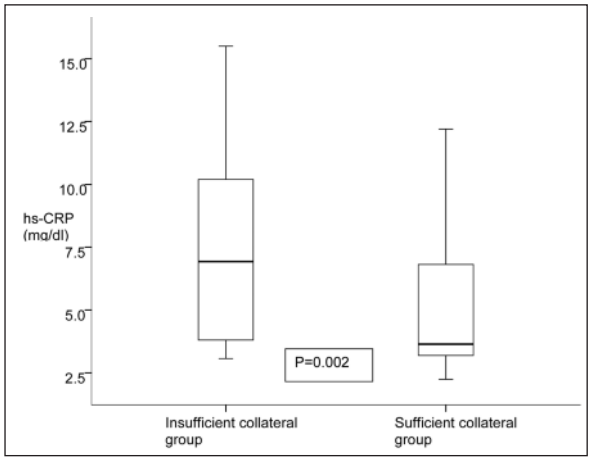

FIGURE 3: High sensitive C-reactive protein levels in the insufficient collateral group and the sufficient collateral groups.
hs-CRP: High sensitive C-reactive protein.

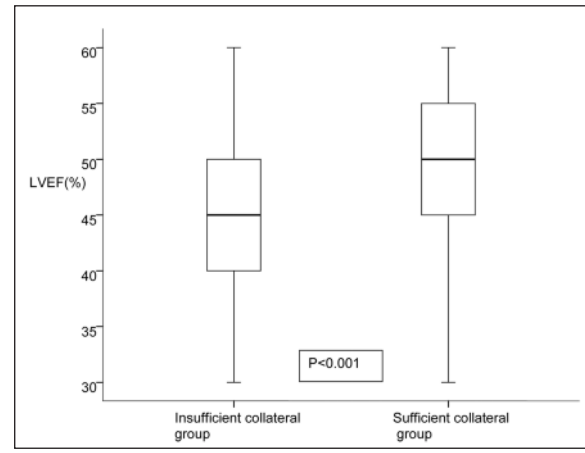

FIGURE 4: Left ventricular ejection fraction values in the insufficient collateral group and the sufficient collateral groups.
LVEF: Left ventricular ejection fraction.

binopathies, hemolysis and hemolytic anemias are often seen with elevated RDW.[16] We did not measure the blood levels of folic acid or vitamin B12 in our patients; however, we excluded from our study patients diagnosed with anemia, patients who had experienced severe hemorrhaging within 3 months prior to coronary angiography or collecting blood and patients who had received a blood transfusion as based on information from the World Health Organization.[17] Pierce and Larson had stated that RDW levels on the upper limit of normal range may be due to the increased immature erythrocytes ratio in circulation blood related to underlying inflammatory situation.[18] Also in our study, consistent with these findings, albeit most of the RDW levels were in the normal range, RDW levels in patients with insufficient CCC group were much higher than patients in the sufficient CCC group. Previous studies have implicated RDW as a strong and independent marker for mortality in a large unselected patient cohort.[4] Tonelli et al. have demonstrated that high levels of RDW independently correlate with cardiovascular incidents, total mortality and development of heart failure in the patient with myocardial infarctions without heart failure. It has been proposed in one study that higher levels of RDW may reflect an underlying inflammatory state.[2] Felker et al. had also stated that high levels of RDW is a strong and independent predictor for mortality and morbidity in the patients with chronic heart failure and they also proposed that high levels of RDW may related with inflammatory cytokines in patients with heart failure.[1] In another study, high levels of RDW are an independent predictor for mortality in patients with stroke history.[19] Further, that study argued that the underlying inflammation was the cause of increased RDW. It has been shown that there is a negative correlation between high levels of CRP and CCC in patients with coronary artery disease and that the increased inflammation is affecting collateral flow development in a negative manner.[20] In our study, the high levels of hs-CRP in patients in the insufficient CCC group compared to the patients in the sufficient CCC group suggests that underlying inflammation is related to increased RDW. Further, other researchers have demonstrated that the levels of RDW correlate with the left ventricular filling pressure and further, it has been suggested that hemodynamics and oxidative stress could be among the possible causes for increased RDW in the patients with heart failure.[3] Fukuta et al. argued that increased RDW levels in the patients with coronary artery disease may related to neurohumoral activation but not inflammation.[21] Additionally, it had been noted that the degree of neurohormonal activation is directly proportional to the severity of the disease in the patients with heart failure.[22] In another study, it was shown that the levels of NT-proBNP increased

when the LVEF and NYHA functional capacity decreased.[23] Vasoactive hormones like angiotensin II and norepinephrine increase the secretion of BNP.[24] Additionally, these neurohormones stimulate erythropoiesis by increasing the production of erythropoietin.[25] In our study, we found high levels of NT-proBNP in the insufficient CCC group compared to the sufficient CCC group. We propose that the higher levels of NT-proBNP concentration in the insufficient group is indicative of increased neurohormonal activity in these patients, as supported by our findings of decreased LVEF in patients with insufficient CCC than patients with sufficient CCC.

CONCLUSION

We found higher RDW levels in patients with insufficient CCC than in patients with sufficient CCC. We hypothesize that high RDW levels in patients with insufficient CCC may be related to both increased neurohormonal activity and increased inflammation.

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