Red Blood Cell Distribution Width (RDW) and its Association with Coronary Atherosclerotic Burden in Patients with Stable Angina Pectoris

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ABSTRACT

Although there are several studies regarding the association between RDW and the vascular events, information is scant about possible role of RDW in cardiovascular system. We aimed to investigate whether RDW is related with the severity and extent of angiographically assessed coronary artery disease (CAD). Two hundred ninety and six stable eligible patients who had undergone coronary angiography with a suspicion of CAD were enrolled consecutively. Two hundred and nine (71%) of 296 patients had CAD (men 70%, mean age±SD: 61±11yrs) and 87 patients (29%) had normal coronary arteries (NCA) without any atherosclerotic lesion (men 48%, 52±11yrs). Red blood cell distribution width values were significantly different among the subgroups determined for the severity and extent of CAD. When 14.8% was accepted as the cut-off value for RDW, the sensitivity and the specificity for the detection of CAD was 68% and 52%. When we performed multiple logistic regression analysis to determine the independent predictors of CAD, we found a positive independent relationship between age, gender, family history of CAD and RDW and CAD. Our results show that RDW has a significant relationship with CAD independent of nonspecific inflammation and circulating inflammatory cells. Although we cannot conclude the underlying pathologic process of RDW, we believe that these findings may pave the way for further studies searching the role of RDW in atherosclerosis.

Key words: *Coronary artery disease, red blood cell distribution width, stable angina pectoris, atherosclerosis*

STABİL ANJİNA PEKTORİSLİ HASTALARDA KIRMIZI KAN HÜCRESİ DAĞILIM GENİŞLİĞİ (RDW) ve KORONER ARTER HASTALIK YÜKÜ ARASINDAKİ İLİŞKİ

ÖZET

Kırmızı kan hücresi dağılım genişliği ve vasküler olaylar arasındaki ilişki ile ilgili bazı çalışmalar olmasına karşın, RDW'nin kardiyovasküler sistemdeki rolü konusunda bilgiler yetersizdir. Bizim amacımız anjiyografik olarak belirlenmiş koroner arter hastalık şiddet ve yaygınlığı ile RDW arasındaki ilişkiyi belirlemektir. Çalışmaya 296 hasta dahil edildi. İki yüz dokuz hastada (71%) KAH tespit edilirken (men 70%, mean yaş±SD: 61±11yıl), 87 hastada (29%) normal koroner arterler görüldü (men 48%, 52±11yıl). Yaş, hipertansiyon, diyabetes mellitus, hiperlipidemi, ailede KAH hikayesi, kreatinine, beyaz kan hücre sayımı, nötrofiller, ve RDW değerleri KAH olan hastalarda normal koronerleri olanlara göre daha yüksekti. Yüksek yoğunluklu lipoprotein KAH olanlarda daha düşüktü. RDW değerleri KAH'nın şiddet ve yaygınlığına göre belirlenmiş alt gruplarda anlamlı derecede farklı idi. Koroner arter hastalığının bağımsız prediktörlerini belirlemek için yaş, cinsiyet, HT, DM, sigara içme, aile hikayesi, HPL, kreatinin, CRP, nötrofil ve RDW'yi içine alan logistik regresyon analizi yaptığımızda, KAH ile yaş, cinsiyet, aile hikayesi ve RDW arasında pozitif bağımsız bir ilişki belirledik. Bizim sonuçlarımız RDW ile KAH arasında dolaşımdaki inflamatuvar hücreler ve nonspesifik inflamasyondan bağımsız olarak önemli bir ilişkiyi gösterdi. Biz RDW'nin aterosklerozdaki altta yatan patolojik durumu sonuçlandıramasak ta; inanıyoruz ki bu bulgular RDW'nin aterosklerozdaki rolünü araştıran çalışmalara zemin hazırlar.

Key words: *Coronary artery disease, red blood cell distribution width, stable angina pectoris, atherosclerosis*

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INTRODUCTION

Red blood cell distribution width (RDW) is a numerical measure of the variability in size of circulating erythrocytes (1). This parameter is routinely reported as part of the complete blood count (CBC), but its use is generally restricted to the differential diagnosis of anemia (2). In a recent study, RDW was significantly related with major cardiac adverse events (MACE) in patients with heart failure even after the adjustment of hematocrit values (3). In another studies, researcher have showed that increased RDW is independently related long-term mortality in patients with coronary artery disease (CAD) without anemia (4,5). But, in these studies, underlying mechanisms related to increased MACE remained unclear. In a last study intended for the pathophysiological mechanism, carotid intima media thickness has been found to be related to RDW in patients with hypertension (6). Although there are several studies regarding the association between RDW and the vascular events, information is scant about possible role of RDW in cardiovascular system. We aimed to investigate whether RDW is related with the severity and extent of angiographically assessed CAD.

MATERIALS AND METHODS

The present study was cross-sectional and observational. Two hundred ninety and six stable eligible patients who underwent coronary angiography with a suspicion of CAD at our institution between October 2009 and June 2010 were enrolled consecutively. All patients have chest pain or angina equivalent symptoms with either positive treadmill test or myocardial perfusion study. Two hundred and nine (71%) of 296 patients had CAD (men 70%, mean age ± SD: 61 ±11yrs) and 87 patients (29%) had normal coronary arteries (NCA) without any atherosclerotic lesion with visual assessment (men 48%, 52±11yrs).

Whole blood count (WBC) and biochemical markers, which were obtained at most within one week before coronary angiography, were used for analyses. Whole blood counts were measured by an automated hematology analyzer (Coulter Gen-S, COULTER Corp, Miami, USA). Absolute cell counts were used in the analyses. Coronary atherosclerotic burden was determined by Gensini's score which considers both the extent and the severity of the lesions at coronary angiography (7). This scoring system grades the stenosis in the epicardial coronary arteries (1 for 1-25% stenosis, 2 for 26-50% stenosis, 4 for 51-75% stenosis, 8 for 76-90% stenosis, 16 for 91-99% stenosis, and 32 for total occlusion) and multiplies this number by a constant number which is determined according to the anatomical position of the lesion.

Patients with congestive heart failure (n=19), recent acute coronary syndrome either with or without ST-segment elevation (within one month before enrollment)(n=53), previous percutaneous coronary intervention (n=23), significant valve disease (n=12), symptomatic peripheral vascular disease (transient ischemic attack, stroke, intermittent claudication, peripheral revascularization, or amputation) (n=17), prior coronary by-pass grafting operation (n=15), congenital cardiac disorders (n=3), cardiomyopathies with dilated or hypertrophic (n=5), chronic kidney disease (serum creatinin<2 mg/dl) (n=13), evidence of ongoing infection or inflammation (WBC>10.000mm-3), hematological disorders including anemia (Hg<12 mg/dl) (n=43), nutritional deficiencies (iron, vitamin B12 and folate deficiency), hyperthyroidism (n=3), hypothyroidism (n=4), known malignancy, isolated coronary artery ectasia (n=9), coronary slow flow (n=13), patients having body mass index (BMI) greater than 42 were excluded from the study.

Statistical analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov-Smirnov test. The Student's t-test was used for the univariate analysis of the continuous variables and the x2 test for the categorical variables. Mean values were compared by ANOVA among different groups. Receiver operating characteristics (ROC) analysis based on the results of coronary angiography after comparing sensitivity and specificity at different cutoff values determined an optimal cut-off for the detection of CAD by RDW. Logistic regression with Enter method was used for multivariate analysis of independent variables. The variables which have significant p values ($p<0.05$) and marginal insignificant p values ($p<0.1$) in univariate analysis were included in the multivariate analysis. All tests of significance were two-tailed. Statistical significance was defined as $P < 0.05$. The SPSS statistical software (SPSS 15.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

Table 1. *Baseline characteristics of the study population*

Groups	NCA (n:87)	CAD		P value
Parameters		<50%(N=83)	≥50%(N=126)	
Gensini score	0±0	2.5±1.9	35±31	<0.001
Age (yrs)	52±11	57±10	63±11	<0.001
Gender (male)	48%	63%	75%	<0.001
Height (cm)	169±6	168±8	170±9	ns
Weight (kg)	83±10	83±13	82±15	ns
BMI (kg/m2)	29±3	29±5	28±4	ns
Waist circumference (cm)	104±16	103±17	105±17	ns
Hypertension	31%	42%	59%	<0.001
Diabetes mellitus	10%	27%	27%	0.008
Smoking	29%	41%	40%	ns
Hyperlipidemia	58%	66%	75%	0.02
Family history of CAD	8%	24%	25%	0.005
Fasting plasma glucose (mg/dl)	109±30	116±36	119±46	ns
BUN (mg/dl)	32±9	36±12	38±14	0.001
Creatinine (mg/dl)	0.81±0.2	0.83±0.2	0.93±0.3	<0.001
Total cholesterol (mg/dl)	203±37	196±45	190±43	ns
LDL (mg/dl)	129±37	123±41	119±35	ns
HDL (mg/dl)	46±13	43±12	41±10	0.03
Triglyceride (mg/dl)	151±80	142±79	148±81	ns
Leukocytes (/mm3)	7349±1601	6892±1603	7534±1556	0.02
Neutrophils (/mm3)	4287±1308	3980±1309	4518±1253	0.01
Lymphocyte (/mm3)	2282±598	2144±663	2172±648	ns
Monocyte (/mm3)	579±268	554±201	600±231	ns
Eosinophil (/mm3)	221±209	189±159	206±135	ns
Basophil (/mm3)	75±31	82±96	79±54	ns
Hemoglobin (mg/dl)	14±1.5	14±1.2	14±1.4	ns
RDW (%)	14.7±1.2	15.2±1.2	15.5±1.3	<0.001
Platelets (103 /mm3)	271±53	276±88	263±58	ns
MPV (fl)	8.7±1.5	8.6±1.4	8.5±1.3	ns
PDW (%)	17.7±1.2	17.7±1.1	17.6±1.5	ns
CRP (mg/dl)	0.59±0.46	0.51±0.57	0.69±0.72	ns
Medications				
Anti-aggregants	15%	39%	51%	<0.001
ACEi/ARB	24%	35%	50%	0.001
Statin	31%	29%	44%	0.05
Beta blockers	17%	19%	42%	<0.001
CCB	8%	13%	12%	ns
Nitrate	5%	4%	4%	ns
OAD/Insulin	11%	25%	26%	0.02

ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; CCB, Calcium channel blocker; CAD, Coronary artery disease; BMI, Body mass index; BUN, blood urea nitrogen; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; NCA, Normal coronary arteries; MPV, mean platelet volume; OAD, Oral anti-diabetic drugs; PDW, Platelet distribution width; RDW, Red blood cell distribution width; CRP, C-reactive protein

***Table 2**. Red blood cell distribution width values in subgroups determined for extent of coronary artery disease.*

	NCA	CAD				
		<50%	≥50% vessels			p value
			1	2	3	
RDW (%)	14.7±1.2	15.2±1.2	15.4±1.2	15.5±1.3	15.7±1.2	<0.001
Gensini score	0±0	2.5±1.9	15.8±15.0	43.1±27.3	64.0±36.8	<0.001
CRP	0.59±0.46	0.51±0.57	0.53±0.42	0.70±0.71	0.95±1.1	0.393
Neutrophils	4287±1308	3980±1309	4407±1039	4602±129	4616±1380	0.054

CAD, Coronary artery disease; NCA, Normal coronary arteries; RDW, Red blood cell distribution width; CRP, C-reactive protein

RESULTS

Distribution of cardiovascular risk factors, demographic characteristics, and laboratory measurements of patients were shown in Table 1. Age (p<0.001), gender (p<0.001), hypertension (HT)(p<0.001), diabetes mellitus (DM)(p=0.008), hyperlipidemia (HPL)(p=0.02), family history of CAD (p=0.005), creatinine (p<0.001), WBC (p=0.02), neutrophils (p=0.01), and RDW values (p<0.001) were higher in patients with CAD than those with NCA. High-density lipoprotein (HDL) was lower in patients with CAD than those with NCA.

Red blood cell distribution width values were significantly different among the subgroups determined for the severity and extent of CAD (NCA and CAD subgroups: <50% luminal obstruction, 1, 2 and 3 diseased vessels≥50%, 14.7±1.2 and 15.2±1.2, 15.4±1.2, 15.5±1.3, 15.7±1.2; p<0.001, repectively)(Table 2). When 14.8% was accepted as the cut-off value for RDW, the sensitivity and the specificity for the detection of CAD was 68% and 52%. When we performed multiple logistic regression analysis including age, gender, presence of HT, DM, smoking, family history, hyperlipidemia, HDL, Creatinine, c-reactive protein (CRP), neutrophils and RDW to determine the independent predictors of CAD, we found a positive independent relationship between age (p<0.001), gender (p<0.001), family history of CAD (p=0.009) and RDW (p=0.03), and CAD (Table 3).

DISCUSSION

This study aimed to investigate whether RDW is related with the severity and extent of CAD. We found that RDW values were significantly higher in the patients with stable CAD compared to the patients with normal coronary arteries at coronary angiography. Increased RDW values were also significantly related with the severity of coronary artery disease. This increase in RDW was found to be independent of other confounding risk factors, and for first time was described in current study.

Red cell distribution width is a marker of the variability in the size of circulating red cells (anisocytosis) and is routinely reported by analysers as part of the routine CBC (1). The formula for RDW is [standard deviation of red cell volume/mean cell volume] x 100. Thus elevated RDW means that there is an increased heterogeneity in size of red cells (RBCs) in the peripheral blood (8,9). Elevated RDW levels can be seen in hemolysis, nutritional deficiencies such as iron, vitamin B12, and folate, or after blood transfusion (10). In thrombotic thrombocytopenic purpura, inflammatory bowel diseases and pregnancy, RDW levels can be high (11). Therefore in the present study, the all known secondary confounding factors for RDW were excluded from study. Thus in the absence of anemia and other secondary confounding factors, the heterogeneity of red blood cell sizes was found to be associated with the severity and extent of CAD.

A recent study was aimed to evaluate the association between RDW and carotid artery atherosclerosis in people with hypertension. A close relationship between high RDW and intima media thickness, and the incidence of carotid plaque was identified (6). This study was only conducted in patients with hypertension and carotid intima media thickness was used to be a surrogate marker for atherosclerosis. In this way, coronary angiographic data was not provided to show clearly the association between RDW and the severity and extent of CAD. Although the relationship between RDW and cardiovascular mortality was determined, the underlying pathophysiological mechanisms have remained unclear.

Table 3. *Multivariate analysis using the logistic regression method for the presence of CAD*

			Logistic regression		
Independent variables	*B*	*SE*	*Wald*	*OR (95% confidence interval)*	*p value**
Age (yrs)	*0.1*	*0.02*	*21*	*1.105 (1.059-1.154)*	*<0.001*
Gender (male)	*1.7*	*0.5*	*14*	*5.400 (2.241-13.013)*	*<0.001*
Hypertension	*0.5*	*0.4*	*1.4*	*1.596 (0.735-3.467)*	*ns*
Diabetes mellitus	*0.7*	*0.5*	*1.7*	*1.985 (0.711-5.547)*	*ns*
Smoking	*0.5*	*0.5*	*1.4*	*1.708 (0.707-4.127)*	*ns*
Family history of CAD	*1.6*	*0.6*	*6.7*	*5.114 (1.509-17.336)*	*0.009*
Hyperlipidemia	*0.1*	*0.5*	*0.1*	*1.076 (0.448-2.583)*	*ns*
RDW	*0.4*	*0.2*	*4.6*	*1.468 (1.034-2.082)*	*0.03*
CRP	*0.1*	*0.7*	*0.1*	*1.081 (0.293-3.983)*	*ns*
Neutrophils	*-0.02*	*0.2*	*0.1*	*0.981 (0.734-1.311)*	*ns*
Creatinine	*-0.2*	*1.2*	*0.1*	*0.806 (0.076-8.587)*	*ns*
HDL	*0.01*	*0.02*	*0.1*	*1.000 (0.968-1.033)*	*ns*

CAD, Coronary artery disease; HDL, High-density lipoprotein; RDW, Red blood cell distribution width; OR, Odds Ratio; CI, Confidence Interval; ; CRP, C-reactive protein; B, Beta Coefficient; SE, Standard error

In these studies, investigators hypothesized that higher RDW levels might reflect underlying chronic inflammation, which would result in higher cardiovascular risk.

At the present time, it is well know that atherosclerosis is chronic inflammatory disease and varied causative cytokines such as TNF-α, IL-1b, and IL-6 are released in its process (11,12). These increased inflammatory cytokines in blood stream may have a suppressing effect on erythropoietin (Epo) and hemoglobin synthesis that this situation causes chronic inflammatory anemia.

Previous studies have demonstrated that inflammatory cytokines could modulate erythropoiesis through two pathways: first, by inhibition of Epo gene transcription at the kidneys and liver; and second, by suppression of erythroid cell maturation at the bone marrow. Research in hypoxic-perfused rat kidney models shows that renal Epo production is vulnerable to suppression by TNF-α, IL-1b, and IL-6, while embryonic hepatoma cell lines are vulnerable to suppression by TNF-α and IL-1b only. Suppression of erythropoiesis occurs in bone marrow by inflammatory cytokine due to blockage of erythroid progenitor cell proliferation and pro-erythroblast maturation. The inflammatory cytokine modulation on bone marrow erythroid progenitors desensitizes the cells to Epo, which blocks its anti-apoptotic and pro-maturation effects (13-15). Therefore, decrease in Epo release causes fewer mature or immature RBCs production and release into circulation. Another possible mechanism is the increased levels of inflammatory cytokines having impacts on iron metabolism and bone marrow function (11,12). RDW is related to the proliferative responses of erythropoiesis and will rise in similar fashion with the reticulocyte count during increased production of immature RBCs (16). In a recent study (17), Gotsman et al. have shown that TNF-α and IL-6 levels are related to Gensini score. In our opinion, these increased cytokines have also destructive and deforming effects on the maturation of erythroid cells, by which they may contribute to increase in RDW levels.

In our study, we found that RDW was related with the severity and extent of CAD independent of CRP and circulating inflammatory cells. This finding is important because shows that RDW might not simply represent chronic non-specific inflammatory status. We applied more specific inclusion and exclusion criterions for the enrolment of patients and our study results may support existence of a more specific relationship between RDW and CAD rather than non-specific relation. On the other hand, in consequence of more intensive medical drug use in our study, the effects of CRP and inflammatory cells on RDW and their relationships with CAD may had been blunted in multivariate analysis. If this speculative opinion is true, no effect of medical drugs on RDW may

be thought, because RDW was related to CAD even after adjusted for all confounding factors.

Of late years, RDW level was searched in patients with chronic heart failure, previous MI, primary PCI and also broad-based community screening studies and found that RDW is related to mortality even in patients without anemia (3-5,18-20). Because all previous studies have provided the mortality and morbidity information related to RDW, novel pathophysiologic insight for underlying mechanisms are still speculative, and there is not any proved evidence for the possible causative role of RDW for the development of CAD and increased all-cause mortality.

Study limitations

Our study had some limitations. First, study population was relatively small. Larger study population would provide higher statistical power. The main limitation of our study is that it does not explain the exact mechanism of relation between elevated RDW values and the severity and extent of CAD. Although we found a relation between RDW and CAD, which is independent of other circulating inflammatory cells, CRP and other CVRFs we do not have any data regarding B-type natriuretic peptide, other pro-inflammatory cytokines, plasma levels of angiotensin II, Epo and markers of oxidative stress. To decrease confounding factors for RDW, we used more extensive specific inclusion and exclusion criterions for the enrolment of patients. However, some confounding factors were significantly different among study groups. Therefore, we performed multiple regression analysis to overcome this issue. Lastly, in our study, control group included the patients who are not completely normal, because although they have angiographically normal coronary arteries they still have cardiac risk factors or may have cardiac syndrome-X. Therefore, the statistical differences would be difficult to determine between normal and pathologic group. Otherwise, our study population proved many significant relations among study groups.

In conclusion, our results show that plasma RDW is significantly higher in patients with CAD. Although we cannot conclude the underlying pathologic process of RDW, we believe that these findings may pave the way for further studies searching the role of RDW in atherosclerosis.

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