ORIGINAL ARTICLE

Coronary artery disease detected by coronary computed tomography angiography is associated with red cell distribution width

Bilgisayarlı tomografi koroner anjiyografisi ile saptanan koroner arter hastalığı kırmızı hücre dağılım genişliği ile ilişkilidir

Emir Karaçağlar, M.D., Uğur Bal, M.D., Senem Hasırcı, M.D., Mustafa Yılmaz, M.D.,# Ersin Doğanözü, M.D., Mehmet Coşkun, M.D.,* İlyas Atar, M.D., Aylin Yıldırır, M.D., Haldun Müderrisoğlu, M.D.

Department of Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey
#Department of Cardiology, Başkent University Faculty of Medicine, Adana, Turkey
*Department of Radiology, Başkent University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: Increased red blood cell distribution width (RDW) is associated with severity of coronary artery disease (CAD). The aim of the present study was to retrospectively evaluate the relationship between CAD detected by coronary computed tomography angiography (CCTA) and RDW.

Methods: Records of 291 patients who underwent 16-slice CCTA due to the presence of angina-like chest pain were retrospectively evaluated. Exclusion criteria were applied. Clinical characteristics, risk factors for CAD, and RDW values on CCTA were noted.

Results: RDW levels in patients with CAD were significantly higher than in those with normal coronary arteries (NCAs) (15.50±1.57 compared to 14.80±1.41, p=0.001). Diabetes mellitus, hypertension, and history of smoking were significantly more common in the CAD group (p=0.018, p=0.007, and p=0.013, respectively). On multivariate logistic regression analysis, RDW (p=0.009 [odds ratio (OR): 1.352; 95% confidence interval (CI): 1.081–1.683]), age (p<0.001 [OR: 1.063; 95% CI 1.031–1.090]), and history of smoking (p=0.003 [OR: 2.672; 95% CI: 1.360–5.232]) were shown to be independent predictors for CAD detected by CCTA.

Conclusion: The present results suggest that higher RDW levels are independently associated with presence of CAD detected by CCTA in patients without known CAD. Further studies are warranted to clarify the exact role of RDW in risk stratification.

ÖZET

Amaç: Kırmızı hücre dağılım genişliği (RDW) artışı koroner arter hastalığı (KAH) ciddiyeti ile ilişkilidir. Bu çalışmanın amacı bilgisayarlı tomografi koroner anjiyografisi (CCTA) kullanılarak saptanan KAH ile RDW arasındaki ilişkiyi geriye dönük olarak değerlendirmektir.

Yöntemler: Anjina veya benzeri göğüs ağrısı nedeniyle 16 kesitli CCTA uygulanan 291 hastanın tıbbi kayıtları geriye dönük olarak incelendi. Dışlama kriterleri olmayan hastalar değerlendirmeye alındı. Hastaların klinik özellikleri, risk faktörleri, CCTA yapıldığı zamanki RDW değerleri incelendi.

Bulgular: Koroner arter hastalarında RDW seviyeleri, koroner arterleri normal olan gruba göre belirgin olarak daha yüksek saptandı (15.50±1.57'ye 14.80±1.41, p=0.001). Diyabet, hipertansiyon ve sigara öyküsü koroner arter hastalığı saptanan grupta daha yüksekti (sırasıyla, p=0.018; p=0.007; p=0.013). Yapılan çok değişkenli lojistik regresyon analizinde, RDW (OO [odds oranı]=1.35, %95 GA (güven aralığı): 1.08–1.68, p= 0.009), yaş (OO=1.06, %95 GA: 1.03–1.09, p<0.001) ve sigara öyküsünün (OO=2.66, %95 GA: 1.36–5.23, p=0.003) CCTA ile saptanan KAH için bağımsız öngördürücüler olduğu saptandı.

Sonuç: Bulgularımız yüksek RDW seviyelerinin, bilinen koroner arter hastalığı olmayan hastalarda CCTA ile saptanan KAH ile ilişkili olduğunu göstermektedir. Riski katmanlandırmada RDW dağılımının rolünü tam olarak açıklığa kavuşturmak için ileri çalışmalara gerek vardır.

Presented at the 83rd Congress of the European Atherosclerosis Society (22-25 March, 2015, Glasgow, UK).

Received: January 13, 2016 *Accepted:* June 28, 2016

Correspondence: Dr. Emir Karaçağlar. Fevzi Çakmak Cad., 10. Sokak. No: 45, Bahçelievler, Ankara, Turkey.
Tel: +90 312 - 212 68 68 e-mail: dremirkaracaglar@hotmail.com

Red blood cell distribution width (RDW) is a measure of variability in the size of circulating erythrocytes, and is mainly used to differentiate the diagnosis of anemia.[1] Elevated levels are associated with coronary artery disease (CAD), both in the stable and unstable form of the disease.[1–3] Tonelli M. et al. examined the association of RDW and the risk of all-cause mortality in a population of patients with coronary disease, and found a graded independent correlation between higher levels of RDW and risk of cardiovascular events.[1] Another study performed among patients with acute coronary syndromes in Portugal showed an independent association between higher RDW values and adverse outcomes.[2] A significant correlation between RDW levels and both presence and severity of CAD detected by conventional coronary angiography has been demonstrated in a large Chinese cohort.[4] However, no data is available regarding the association between CAD detected on coronary computed tomography angiography (CCTA) and RDW.

Abbreviations:

CAD	*Coronary artery disease*
CCTA	*Coronary computed tomography angiography*
CI	*Confidence interval*
Hb	*Hemoglobin*
LDL	*Low-density lipoprotein*
NCA	*Normal coronary artery*
OR	*Odds ratio*
RDW	*Red blood cell distribution width*

The present aim was to evaluate the potential correlation of RDW and the presence of CAD (detected by CCTA) among our patients.

METHODS

Study population included 291 patients who underwent clinically indicated CCTA due to presence of angina-like chest pain between January 2012 and February 2014. Records were retrospectively evaluated. Patients with known CAD (n=58), known hematological disease (n=11), history of heart failure (n=5), renal dysfunction (serum creatinine levels ≥1.5 mg/dL) (n=2), hepatic insufficiency (n=1), ongoing infection (n=1), concomitant cancer (n=0), or systemic inflammatory conditions (n=0) were excluded.

Remaining patients were divided into 2 groups based on the results of CCTA: those with CAD and those with normal coronary arteries (NCAs). CAD was defined as any degree of stenosis in any coronary artery.

Baseline characteristics of all patients, including age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking history, left ventricular wall motion abnormality, and laboratory parameters upon CCTA (including creatinine, low-density lipoprotein [LDL], hemoglobin [Hb], and RDW) were noted, as was use of any medication.

RDW determination

Blood samples were obtained after a 12-hour overnight fast. RDW levels were measured by an automated hematology analyzer (Cell-Dyn 3700 system; Abbott Diagnostics, Inc., Santa Clara, CA, USA).

CCTA procedure

Scans were performed using 16-slice multidetector computed tomography scanner (Somatom Sensation 16; Siemens AG, Munich, Germany). Patients with initial heart rates of ≥70 beats/min were administered medication to lower this rate (beta-blockers, nondihydropyridine calcium channel blockers, etc.) according to medical features. Sublingual nitroglycerine (0.4 mg) was administered to dilate the coronary arteries 1 minute prior to contrast injection. Scans were obtained after injection of 90–120 mL non-ionic contrast agent (ioversol injection; Optiray Pharmacy Bulk Package; Liebel-Flarsheim Company, LLC., Raleigh, NC, USA) at a flow rate of 5 mL/s. All images were interpreted immediately after scanning by an experienced radiologist, in accordance with the Society of Cardiovascular Computed Tomography guidelines on coronary CTA interpretation.[5]

Statistical analysis

Statistical analysis was performed using SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±SD. Categorical variables were expressed as percentages.

All continuous variables were checked with Kolmogorov–Smirnov normalcy test to demonstrate distribution. Continuous variables with normal distribution were compared using unpaired Student's t-test. Continuous variables with abnormal distribution, such as Hb and LDL, were compared using Mann–Whitney U test. Chi-square test was used to compare categorical variables. To determine the independent predictors of presence of coronary atherosclerosis, multiple logistic regression analysis was performed by including univariate parameters with a p value of less than 0.1 between groups. A p value of less than

0.05 was considered statistically significant. The present study was approved by the local institutional review board (project no: KA14/275).

RESULTS

Study population included 213 patients who underwent CCTA and did not meet exclusion criteria. Mean age was 54.8±12.5 years and 47.4% of patients were female. The population was divided into 2 groups based upon CCTA results. CAD was detected in 97 (45.5%) of the 213 patients, and NCAs were found in 116 (54.5%).

Clinical characteristics, medications, and laboratory parameters are shown in Table 1. Diabetes mellitus, hypertension, history of smoking, and hyperlipidemia were significantly more common in the CAD group (p=0.018, p=0.007, p=0.013, and p=0.047, respectively). Gender distribution, creatinine, LDL, and Hb levels were similar between groups. Left ventricular wall motion abnormality was not observed. Mean RDW level was 15.50±1.57% in the CAD group, and 14.80±1.41% in the NCA group. RDW levels in patients with CAD were significantly higher, compared to the NCA group (15.50±1.57, compared to 14.80±1.41, p<0.001). Among medications patients were already

Table 1. Patient characteristics and laboratory findings

Variables	CAD group (n=97)	NCA group (n=116)	*p*
Age (years)	58.6±11.79	50.5±11.98	<0.001
Male, n (%)	51 (52.5)	61 (52.6)	0.999
Smoking history, n (%)	38 (39.1)	27 (23.2)	0.012
Diabetes mellitus, n (%)	18 (18.5)	9 (7.8)	0.018
Hypertension, n (%)	54 (55.6)	43 (37.1)	0.007
Hyperlipidemia, n (%)	42 (43.2)	35 (30)	0.047
Medication			
Acetylsalicylic acid, n (%)	35 (36.1)	15 (12.9)	<0.001
ACE inhibitors/ARBs, n (%)	45 (46.4)	30 (25.9)	0.002
□-blockers, n (%)	25 (25.8)	29 (25.0)	0.897
Statins, n (%)	23 (23.7)	13 (11.2)	0.015
Laboratory parameters			
Median Hb (g/dL) (minimum—maximum)	13.8 (12.7–18.2)	13.6 (12.9–16.7)	0.467
Red blood cell distribution width (%)	15.5±1.57	14.8±1.41	<0.001
Median LDL (mg/dL) (minimum—maximum)	140.5 (50–225)	134 (43–255)	0.726
Creatinine (mg/dL)	0.9±0.40	0.8±0.15	0.270

ACE: Angiotensin-converting-enzyme; ARB: Angiotensin-receptor blocker; CAD: Coronary artery disease; EF: Ejection fraction; Hb: Hemoglobin; LDL: Low-density lipoprotein; NCA: Normal coronary artery.

Table 2. Predictors of CAD detected by CCTA in multivariate logistic regression analysis

Variable	Odds ratio	95% Confidence interval	*p*
Age	1.063	1.031–1.090	<0.001
Smoking history	2.672	1.360–5.232	0.003
Diabetes mellitus	1.741	0.682–4.451	0.533
Hypertension	1.264	0.653–2.431	0.944
Hyperlipidemia	1.450	0.772–2.721	0.943
Red blood cell distribution width	1.352	1.081–1.683	0.009

CAD: Coronary artery disease; CCTA: Coronary computed tomography angiography.

using, acetylsalicylic acid, angiotensin-converting-enzyme inhibitors/angiotensin-receptor blockers, and statin were significantly more common in the CAD group (p<0.001, p=0.009, and p=0.032, respectively). It was determined that age (p<0.001 [odds ratio (OR): 1.063; 95% confidence interval (CI): 1.031–1.090]), smoking history (p=0.003 [OR: 2.672; 95% CI: 1.360–5.232]), and RDW levels were independently associated with the presence of CAD (p=0.009 [OR: 1.352; 95% CI: 1.081–1.683]) (Table 2).

DISCUSSION

In this present study, an independent correlation between RDW, age, smoking history, and presence of CAD on CCTA was demonstrated in patients without previous diagnosis of CAD.

As expected, diabetes mellitus, hypertension, hyperlipidemia, and smoking history were also significantly more common in the CAD group, as had been observed in previous studies.[4] However, interestingly, only age, history of smoking, and RDW levels were presently found to be independently correlated with the presence of CAD. Unexpectedly, LDL levels were similar between groups (137.51±37.68 compared to 139.23±51.52 mg/dL, p=0.798), which may be explained by the higher rate of statin use in the CAD group (23.7% compared to 11.2%, p=0.032). Exact effects of medication on RDW could not be evaluated using the present results. Reported effects of statins on RDW differ. Zalawadiya et al.[6] reported a negative association between statin use and RDW. A more recent study that investigated the effects of atorvastatin on hematologic parameters in patients with hypercholesterolemia found no significant change after atorvastatin treatment.[7] Effects of medications on RDW cannot presently be discussed, as pre-treatment RDW levels, and duration and dosage of medication were not available.

Many studies have shown that RDW is closely related to prognosis and long-term adverse events of cardiovascular diseases. Felker et al. described an independent prognostic value of RDW in heart failure patients.[8] Another study reported a significant association between RDW levels and all-cause mortality in cases of stable CAD.[1] An independent correlation was also demonstrated between RDW level, fatality, and recurrent myocardial infarction within 6 months in patients with acute coronary syndrome.[2] Recent studies have suggested a positive correlation between all-cause mortality and incidence of adverse events in unselected outpatients.[9,10]

Presently investigated was the relationship between RDW and presence of CAD on CCTA. Significantly higher RDW levels were found in the CAD group, compared to the NCA group. Furthermore, RDW was found to be an independent predictor for presence of CAD on CCTA. The present findings are compatible with those of a previous study, in which the relationship of RDW levels and severity of CAD on conventional coronary angiography was investigated.[4] We believe that the present findings may be more significant. While conventional coronary angiography is only lumenography, CCTA is more helpful in the detection of lesions that do not cause luminal narrowing.

The exact mechanism of the correlation between RDW and CAD remains unclear, and several hypotheses have been proposed. A probable primary mechanism is inflammation.[9–12] Atherosclerosis is described as an inflammatory disease, and inflammatory markers such as C-reactive protein and interleukin-6 are closely related to the presence and severity of CAD.[1,13] A strong association between RDW and inflammatory markers was demonstrated in a large cohort of unselected adult outpatients, and also in patients with inflammatory bowel disease.[7] In addition, inflammatory cytokines inhibit the maturation of red blood cells, and immature erythrocytes enter circulation, causing an increase in heterogeneity and resulting in elevated RDW.[14]

Study limitations

Several limitations were present. This was a single-center retrospective study, and prospective multicenter studies are needed to clarify the exact role of RDW in CAD. No data regarding plaque morphology (calcification, lipid core width, etc.) or coronary calcium score were included. In addition, normal CCTA cannot rule out other coronary syndromes such as microvascular angina, coronary syndrome X, etc. While no patient had hematological disease, and none were anaemic, other factors that may effect RDW (iron, vitamin B12, folate, etc.) were not measured. Finally, due to ethnicity, the present results cannot be generalized to all populations.

In conclusion, higher RDW levels were independently associated with presence of CAD detected by CCTA in patients without known CAD. Further studies are needed to clarify the exact role of RDW in risk stratification.

Conflict-of-interest issues regarding the authorship or article: None declared

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Keywords: Biomarkers; coronary artery disease; coronary computed tomography angiography; red blood cell distribution width.

Anahtar sözcükler: Biyobelirteçler; koroner arter hastalığı; koroner bilgisayarlı tomografik anjiyografi, kırmızı hücre dağılım genişliği.