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Higher red cell distribution width values are associated with impaired exercise capacity during exercise treadmill testing in patients without obstructive coronary disease: a preliminary study

C. BARCIN, M. CELIK, U.C. YUKSEL, H.K. KABUL, Y. GOKOGLAN, E. YALCINKAYA[1], S. YASAR

Department of Cardiology, Gulhane Military Medical Academy, School of Medicine, Ankara, Turkey
[1]Department of Cardiology, Aksaz Military Hospital, Mugla, Turkey

Abstract. – BACKGROUND: Red cell distribution width (RDW) is associated with poor cardiovascular outcomes. We aimed to find out if this association could be explained by impaired exercise capacity in patients without obstructive coronary artery disease (CAD).

PATIENTS AND METHODS: The patients who underwent exercise treadmill test (ETT) who have non-obstructive CAD and were free of heart failure symptoms were evaluated. Total of 132 patients were enrolled, and patients were divided into three groups according to their Metabolic Equivalent Task (MET) level measured by exercise treadmill test (ETT): Less than 7 METs (group 1), 7-10 METs (group 2) and greater than 10 METs (group 3).

RESULTS: The patients in Group 1 had significantly higher RDW levels (16.46 ± 2.79) compared to Group 2 (15.05 ± 2.03) and Group 3 (14.52 ± 1.37), independent of hemoglobin and hematocrit values. Significant differences for age, gender, duration of ETT and Duke Treadmill Score were also found in proportion to the reduced exercise capacity. In multivariate analysis, only duration of ETT ($\beta = 1.017$, $p = < 0.001$) and RDW ($\beta = 0.040$, $p = 0.026$) were found as independent variables, which had statistically significant effects on METs.

CONCLUSIONS: We found an independent association between RDW and exercise capacity in patients free of obstructive coronary disease suggesting that patients with elevated RDW values are expected to have impaired exercise capacity.

Key Words:
Red cell distribution width, Exercise capacity, Coronary artery disease, Exercise treadmill test, Duke Treadmill Score.

Introduction

Reduced exercise capacity can considerably impair quality of life and the assessment of exercise capacity is an important element in the evaluation of patients with coronary artery disease (CAD). Exercise capacity can be estimated by numerous methods. Exercise treadmill testing (ETT) is a cost effective, well established and most commonly used noninvasive diagnostic tool in the evaluation of patients with suspected or known CAD. Although the main weight has given to the diagnostic value of ST-segment depression, ETT also provides important diagnostic and prognostic data on the exercise capacity. Metabolic equivalent of task (MET) levels can be easily obtained from the ETT protocols.

Red cell distribution width (RDW), which automatically performed as a part of a complete blood count represents the numerical value of the variability in the size of circulating erythrocytes and generally used as an indicator of the differential diagnosis of anemia[1]. Although elevated RDW levels indicate impaired production or increased destruction of red blood cells[2], several recent large clinical studies have shown that elevated RDW level is also related to adverse clinical outcomes in various cardiovascular diseases, independent of hemoglobin and/or hematocrit values[3-12]. However, the underlying pathophysiological mechanism responsible for this association has not been fully elucidated.

We hypothesized that elevated RDW might reflect pathophysiologic conditions that may lead to impaired exercise capacity and investigated whether RDW was independently associated with the exercise capacity in patients who undergone ETT due to clinical suspicion of CAD.

Patients and Methods

Patients

We retrospectively evaluated the patients who had necessary data and underwent ETT for sus-

Corresponding Author: Emre Yalcinkaya, MD; e-mail: dremreyalcinkaya@gmail.com

pected CAD between February and August 2013. All patients had an initial evaluation consisting of history, physical examination, 12-lead ECG, complete blood count analysis and then ETT. The patients with recent acute myocardial infarction, with the signs and symptoms of congestive heart failure, having obstructive lesion in any coronary artery detected in coronary angiography performed due to positive ETT results, mechanical prosthetic valves, infective endocarditis, low left ventricular ejection fraction (< 50%), nutritional deficiency (iron, vitamin B12, or folate deficiency), blood dyscrasias, recent blood transfusion, autoimmune or inflammatory diseases, renal failure and hepatic failure were excluded. A total of 285 patients were evaluated, and 153 patients matching the above exclusion criteria were excluded from the study. The remaining 132 patients were finally included in the analysis.

Exercise Treadmill Test

After discontinuation of drugs, which possibly affect the ETT results such as beta-blockers and long acting nitrate agents, a symptom-limited ETT using Bruce protocol was performed according to established guidelines[13]. The ETT was considered diagnostic if the patient reached target heart rate (85 % of the maximum predicted heart rate), or typical angina symptoms developed during the test. An up-sloping ST depressions ≥ 1.5 mm or down sloping/horizontal depressions ≥ 1.0 mm in at least 2 leads were accepted as positive ETT. The same independent investigator blinded to patients' clinical details and biochemical results analyzed all ETT results. MET level and Duke Treadmill Score (DTS) were calculated from the ETT protocols. Patients were divided into 3 groups according to their exercise capacity estimated by ETT: Group 1, poor exercise capacity (< 7 METs); Group 2, moderate exercise capacity (7-10 METs); and Group 3, good exercise capacity (> 10 METs).

Laboratory Measurements

The blood samples were taken in the morning hours after a fasting period of at least 12 hours within a week of ETT. The blood samples for complete blood count analysis were collected in tripotassium EDTA tubes and analyzed using an automatic blood counter. Routine biochemical tests including fasting plasma glucose, creatinine, blood urea nitrogen, total serum cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein cholesterol were also measured.

Statistical Analysis

The data were tested for normal distributions using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as means ± standard deviation (SD). The categorical variables were presented as percentages. To compare the continuous variables among 3 groups, one-way analysis of variance (ANOVA) test was used. When significant differences were detected among the 3 groups, Bonferroni or Tukey was used as post-hoc test to delineate pair-wise differences. Chi-squared test was used to compare the categorical variables. Differences were considered statistically significant when p value < 0.05. Pearson was used to test univariate correlation with RDW. Following univariate correlations, a multivariate linear regression model with backward selection process was applied to identify independent predictors of RDW. The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 20 was used for all statistical analyses and calculations.

The Institutional Ethics Committee approved the study protocol, and the study was conducted in accordance with the Declaration of Helsinki.

Results

Baseline demographic and clinical characteristics as well as risk factors were similar in the three groups, except for age and gender. The age of patients with poor (group 1) and moderate exercise capacity (group 2) was significantly higher than those of good exercise capacity (group 3). A gender difference was also observed between three groups suggesting that exercise capacity was significantly higher in males than females. As expected, the duration of ETT and Duke Treadmill Score were found to be decreased in proportion to the reduced exercise capacity. Patients with poor exercise capacity (group 1) demonstrated significantly higher RDW levels (16.46 ± 2.79) compared to moderate (15.05 ± 2.03) and good exercise capacity (14.52 ± 1.37), independent of hemoglobin and/or hematocrit values. The other hematologic and biochemical parameters were similar in the three groups. Baseline demographic and clinical characteristics, as well as laboratory and ETT results of the groups are presented in Table I.

In univariate correlation analysis, age, sex, body mass index, hypertension, exercise duration, Duke treadmill score, creatinine, hemoglo-

Table I. Baseline demographic features, clinical characteristics, laboratory and ETT results of the groups with different exercise capacity.

	All patients (n = 132)	Group 1 (n = 33) (< 7 METs)	Group 2 (n = 32) (7-10 METs)	Group 3 (n = 67) (>10 METs)	p value
Age, y, mean ± SD	53.47 ± 11.92	53.63 ± 15.42	59.28 ± 10.38	50.62 ± 9.57	0.003
Male sex, n (%)	49 (37.1%)	7 (21.2%)	9 (28.1%)	33 (49.3%)	0.012
Body mass index, kg/m^2, mean ± SD	28.55 ± 4.60	29.93 ± 5.02	28.94 ± 4.88	27.68 ± 4.09	0.060
Diabetes, n (%)	29 (22%)	6 (18.2%)	11 (34.4%)	12 (17.9%)	0.150
Hypertension, n (%)	57 (43.2%)	19 (57.6%)	13 (40.6%)	25 (37.3%)	0.149
Hyperlipidemia, n (%)	19 (14.4%)	5 (15.2%)	3 (9.4%)	11 (16.4%)	0.640
Previous CAD, n (%)	27 (20.5%)	7 (21.2%)	7 (21.9%)	13 (19.4%)	0.953
Medications					
ASA, n (%)	37 (28%)	11 (33.3%)	11 (34.4%)	15 (22.4%)	0.340
ACEI/ARB, n (%)	29 (22%)	8 (24.2%)	8 (25%)	13 (19.4%)	0.768
BB, n (%)	29 (22%)	11 (33.3%)	8 (25%)	10 (14.9%)	0.100
CCB, n (%)	14 (10.6%)	4 (12.1%)	4 (12.5%)	6 (9%)	0.821
Statin, n (%)	13 (9.8%)	5 (15.2%)	1 (3.1%)	7 (10.4%)	0.259
Exercise Treadmill Test					
Duration, min, mean ± SD	8.20 ± 3.83	3.83 ± 1.21	7.11 ± 0.83	10.86 ± 2.09	< 0.001
METs, mean ± SD	10.05 ± 3.47	5.87 ± 1.16	8.70 ± 0.92	12.77 ± 2.40	< 0.001
Maximum Heart Rate (reached), (%)	97.25 ± 9.42	93.72 ± 12.43	99.71 ± 9.39	97.82 ± 7.11	0.028
Duke Treadmill Score	-0.2 ± 8.30	-5.11 ± 6.91	-2.50 ± 6.47	3.65 ± 8.01	< 0.001
Biochemical parameters (Plasma)					
Fasting glucose, (mg/dl)	108.90 ± 31.62	107.80 ± 20.63	118.51 ± 45.46	105.07 ± 27.81	0.161
Urea (mg/dl)	30.23 ± 7.98	30.58 ± 8.42	31.48 ± 8.72	29.50 ± 7.45	0.524
Creatinine (mg/dl)	0.92 ± 0.17	0.89 ± 0.13	0.89 ± 0.19	0.96 ± 0.18	0.111
HDL-C, (mg/dl)	48.02 ± 11.11	49.23 ± 12.42	46.96 ± 9.43	47.87 ± 11.23	0.743
LDL-C, (mg/dl)	124.93 ± 38.29	127.46 ± 48.59	130.59 ± 37.33	121.00 ± 32.58	0.518
Triglyceride, (mg/dl)	153.04 ± 109.17	177.77 ± 115.08	160.35 ± 137.14	136.85 ± 88.79	0.220
Total-C, (mg/dl)	200.85 ± 42.22	208.80 ± 53.94	202.28 ± 37.97	196.08 ± 37.00	0.391
Hematological parameters					
White blood cell, (10^3 / μL)	6.17 ± 2.10	6.16 ± 1.89	6.60 ± 3.07	5.96 ± 1.55	0.364
Red blood cell, (10^3/μL)	4.67 ± 0.46	4.73 ± 0.45	4.57 ± 0.43	4.70 ± 0.47	0.300
Hemoglobin, (g/dL)	13.45 ± 1.30	13.24 ± 1.37	13.25 ± 1.24	13.65 ± 1.28	0.214
Hematocrit, (%)	40.45 ± 4.84	39.99 ± 3.90	39.77 ± 3.19	41.00 ± 5.80	0.407
Mean Corpuscular Volume,	86.28 ± 4.74	85.12 ± 3.97	86.31 ± 6.45	86.83 ± 4.05	0.236
Red cell distributed width (%)	15.13 ± 2.11	16.46 ± 2.79	15.05 ± 2.03	14.52 ± 1.37	< 0.001
Platelet count, (10^3/μL)	265.14 ± 63.37	275.18 ± 59.62	276.28 ± 56.18	254.88 ± 67.44	0.168
Mean platelet volume, (fL)	8.81 ± 0.86	8.77 ± 0.89	8.85 ± 0.93	8.82 ± 0.82	0.933
Neutrophil/Lymphocyte ratio	1.88 ± 0.86	1.87 ± 0.80	1.75 ± 0.49	1.96 ± 1.02	0.559

CAD: coronary artery disease; ASA: acetylsalicylic acid; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BB: beta blocker; CCB: calcium channel blocker; METs: The metabolic equivalent; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; Total-C: total serum cholesterol.

bin and RDW were found significantly correlated with METs. The correlation between METs and RDW is demonstrated in Figure 1. To determine the variables independently associated with METs levels, a backward multivariate linear regression model, including variables that correlated significantly with METs and those that exhibited significant differences between 3 groups, was performed. In multivariate analysis, only duration of ETT (β = 1.017, p = < 0.001) and RDW (β = 0.040, p = 0.026) were found as independent variables, which had statistically significant ef-

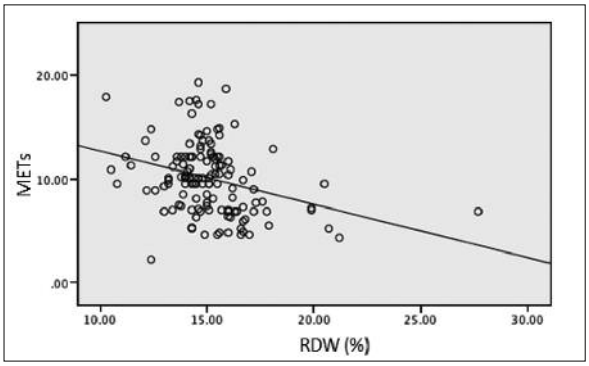

Figure 1. Correlation between Metabolic Equivalent Task (METs) and Red cell distribution width (RDW).

fects on METs. The results of univariate and multivariate linear regression analysis are presented in Table II.

Discussion

In the present study, we found a graded independent relation between levels of RDW and exercise capacity in patients free from critical CAD and heart failure.

The exercise capacity has long been used as a reliable predictor of cardiovascular and overall mortality and morbidity[14]. The exercise capacity is often evaluated in MET concept, which is frequently used to indicate the aerobic intensity and quantify the energy or oxygen cost of various physical activities performed by a person[13]. In practice, the exercise capacity has been classified as excellent (higher than 10 METs), good (7-10 METs), moderate (4-7 METs), and poor (less than 4 METs)[15]. MET levels are easily calculated from the treadmill-based ETT protocols and provide an objective estimate of exercise capacity without requiring additional equipment or cost. Dunagan et al[14] showed that the ETT is providing an exercise capacity assessment equivalent to the Duke Activity Status Index and objective physiologic measures for developing exercise prescriptions and measuring progress. Many factors such as age, gender, body mass index, body fat composition, hemoglobin content, renal function, the heart size, peak heart rate and stroke volume, which lead to a decrease in maximal workload achieved or maximal oxygen consumption have been reported affecting exercise capacity[16-19].

RDW reflects heterogeneity in the size of circulating red cells and RDW levels commonly rise as a consequence of conditions that contribute to increased red cell destruction (such as hemolysis), impaired erythropoiesis, nutritional deficiency (iron, vitamin B12, or folate deficiency) and recent blood transfusion[20]. Patients with these confounders were excluded from the study. Recent studies found a strong independent association between elevated RDW levels and adverse cardiovascular clinical outcomes including all-cause mortality in patients with cardiovascular diseases, especially among patients without anemia[21]. In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) study of 2679 heart failure patients, among routine biochemical and hematologic measures, elevated RDW level exhibited the greatest relationship with morbidity and mortality[4]. Correspondingly, in their study of 4111 stable CAD patients without heart failure, Tonelli et al[8] found a graded independent association between elevated RDW levels and the risk of death and adverse cardiovascular events. In addition, elevated RDW levels were found as a powerful independent risk factor for future cardiovascular disease in healthy individuals[22]. The exact mechanism through which elevated RDW level is associated with poor cardiovascular outcomes has not been fully elucidated. In the present study, we aimed to examine the relationship between RDW and exercise capacity in order to explain the underlying mechanism.

The relationship between RDW and exercise capacity has not been fully elucidated in literature. Only one study by Craenenbroeck et al[23] showed

Table II. Univariate and Multivariate regression analysis based on independent variables likely to affect the METs.

Independent variables	Univariate analysis		Multivariate analysis	
	β	*p*	β	*p**
Age	-0.207	0.017	-0.023	0.202
Gender	-0.312	< 0.001	0.008	0.735
BMI	-0.302	< 0.001	-0.019	0.300
HT	-0.185	0.034	0.023	0.190
Exercise duration	0.975	< 0.001	1.017	< 0.001
Reached MHR	0.078	0.312	0.001	0.934
Duke Treadmill Score	0.503	< 0.001	-0.037	0.063
Creatinine	0.183	0.042	-0.017	0.378
Hemoglobin	0.202	0.020	0.022	0.189
RDW	-0.314	< 0.001	0.040	0.026

**p* value at the last step, which the independent variables remained in model. BMI: body mass index; HT: hypertension; MHR: maximum heart rate; RDW: red cell distribution width.

that higher RDW is independently related to impaired exercise capacity in CHF patients. In the present study, we examined the relationship between RDW levels and exercise capacity defined by METs in patients without obstructive coronary artery stenosis and heart failure and found a graded and independent association between baseline RDW level and exercise capacity, even after adjustment for multiple potential confounders. Although age and gender were different in the groups with various exercise capacity, these parameters were not independently predictive of METs achieved in multivariate regression analysis.

Taken together, the underlying mechanism of poor clinical outcomes in patients with higher RDW may be related to the decrease in exercise capacity. The mechanism and the direction of this potential association as well as the factors that increase the RDW are not yet fully clear. Speculating that raised RDW is the "cause" of decreased exercise capacity rather than a "surrogate marker" of it, inflammation, which is one of the hallmarks of atherosclerosis, may play a role in increased RDW levels, and consequently, impaired exercise capacity in patients with CAD. Cardiovascular diseases have a recognized relationship with the inflammatory markers[24]. Importantly, a strong correlation between RDW and inflammatory markers, C-reactive protein and sedimentation rate has been detected[5,25]. Inflammatory cytokines have been found to suppressing the erythrocyte maturation, disturbing the red cell membrane, allowing juvenile erythrocytes entering into circulation and, therefore, increasing in heterogeneity of the size and RDW levels[26,27]. The other most common proposed mechanism for increased RDW level is neurohumoral activity. Experimental and clinical studies have reported an association between accelerated erythropoiesis and activation of neurohumoral states (the sympathetic system and renin-angiotensin system), which may in turn increase RDW[28,29]. Consequently, the survival of red blood cell is reduced by ineffective erythropoiesis due to both chronic inflammation and neurohumoral activation, juvenile erythrocytes are released into the circulation and therefore the delivery of oxygen to the tissues is reduced, especially during exercise[30]. Consistent with these mechanisms, in the present study, we found that RDW independently predicts the exercise capacity in patients without severe CAD and heart failure. The clinical impact of this relationship, on the other hand, is not exactly known and should further be evaluated.

Conclusions

In patients without obstructive CAD as well as heart failure, relatively higher RDW values are related to lower exercise capacity. This potential relationship between RDW and exercise capacity can provide an insight into understanding the underlying mechanism of poor clinical outcomes in patients with cardiovascular disease. Further studies are required to explain this relationship in more detail.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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