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Research Article

Red Blood Cell Distribution Width in Obstructive Sleep Apnea Syndrome and its Association with Cardiovascular Disease

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ABSTRACT

Background: Red Blood cell distribution Width (RDW) is reported as a novel marker of Cardiovascular Disease (CVD) risk. We aimed to investigate the correlation of RDW level with the severity of Obstructive Sleep Apnea Syndrome (OSAS) defined with the Apnea Hypopnea Index (AHI) and to study the relationship between RDW and CVD in OSAS.

Results: From retrospective analyses of patients admitted to our department for polygraphy between January 2018 and January 2020, OSAS patients with complete medical records and hemogram analyses were evaluated. The study population consisted of 160 patients (101 females/59 males). The mean age was 52.32 ± 10.83 years. RDW correlated positively with the Apnea Hypopnea Index (AHI) (r=0.392; p<0.0001) and CRP (r=0.3, p<0.001). RDW and CRP were significantly higher in patients with CVD than whom without CVD (p <0.0001). In multivariate analysis, the independent predictors of CVD in OSAS were RDW (p<0.0001; OR=3.095; CI: 1.69-5.66), CRP (p=0.046; OR=1.136; CI: 1.002-1.287) and age (p=0.013; OR=1.085; CI: 1.017-1.157). The cut-off level for RDW with optimal sensitivity and specificity was calculated as 14.45 with sensitivity of 81% and specificity of 75%.

Conclusions: The findings of this study suggest that RDW, a simple, relatively inexpensive and universally available marker could have the ability to predict CVD in OSAS.

Keywords: Apnea-hypopnea index; Red blood cell distribution width; Obstructive sleep apnea syndrome; Cardiovascular disease

INTRODUCTION

Obstructive Sleep Apnea Syndrome (OSAS) is a chronic condition characterized by repeated episodes of upper airway obstruction during sleep, which lead to intermittent arterial oxygen desaturation, hypercapnia, arousals, and sleep disruption [1]. OSAS has been established as an independent risk factor for the development of cardiovascular events such as coronary artery disease, hypertension and myocardial infraction [2-4]. OSAS predisposes to Cardiovascular Disease (CVD) through several proposed mechanisms: Sympathetic excitation, altered vascular regulation, endothelial dysfunction, oxidative stress and chronic systemic inflammation caused by recurrent intermittent hypoxia [5]. In addition to the mentioned mechanisms, various conditions associated with OSAS such as obesity and hyperlipidemia increase the risk of CVD [6]. Several studies reported that frequency of cardiovascular complications of OSAS increases with severity of the disorder [3]. Red Blood cell distribution Width (RDW), a numerical measure of the size variability of circulating erythrocytes, is known as a possible pathogenic link in CVD. The normal reference range of RDW for human red blood cells is 11% to 15% [7,8].

In a simplistic way, higher RDW results of greater heterogeneity and disparity between the sizes of Red Blood Cells (RBCs) altering blood flow dynamics. Therefore, RDW is reported as a marker of CVD risk. Considering the association between OSAS and CVD, we aimed to investigate the correlation of RDW level with the severity of OSAS defined with the Apnea Hypopnea Index (AHI) and to study the relationship between RDW and CVD in OSAS.

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MATERIALS AND METHODS

Characteristics of the patients

Demographic characteristics (age, sex, Body Mass Index [BMI], current cigarette smoking status, history of preexisting diseases, and current drug use), sleep history, and medical history, including cardiovascular and metabolic diseases, medication use, and habits were obtained from medical records. CVD were defined if patients had hypertension, coronary artery disease, arrythmia, valvopathy or heart failure. Anemia was defined as hemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men.

The exclusion criteria were as follows: patients who had central sleep apnea syndrome, lung disease with hypoxemia, cerebrovascular disease, anemia, chronic renal or hepatic diseases, use of sedatives and muscle relaxants, a history of recent blood transfusion (2 weeks), and known hematologic disease such as leukemia or myelodysplastic syndrome.

Respiratory polygraphy

All participants underwent a respiratory polygraphy (Nox-T3) over a night period of at least six hours including: measurement of blood oxygen saturation by oximetry and oronasal airflow, quantification of snoring with recording of noises tracheal and position analysis. Polygraphy recordings were scored according to the criteria of the American Academy of Sleep Medicine. Apnea was defined as complete cessation of airflow at least 10 seconds. Hypopnea was defined as reduction of more than 30% the airflow signal with an associated fall of at least 3% in oxygen saturation. AHI was defined as the number of apneas and hypopneas per hour of sleep. Patients with AHI at least 5 events per hour were diagnosed as having OSAS. According the American Academy of Sleep Medicine, patients were grouped into three OSAS severity groups based on the AHI: mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI>30).

Measurement of RDW

Data on blood cell counts including RDW were obtained from medical records retrospectively. Blood cell counts were determined using an automated blood cell counter (Hematology Analyzer Coulter LH 750, Beckman Coulter).

Statistical analyses

Statistical analyses were performed with SPSS version 20.0 software (SPSS Inc, Chicago, Illinois, USA). Simple descriptive statistics such as mean and standard deviation or percentage were calculated for continuous or categorical data. The chi-squared test and the one-way ANOVA test were used to examine the differences in characteristics between the groups. Pearson's correlation analysis was performed to determine the strength of relationship of continuous variables.

A logistic regression analysis model was used to compare the association between independent variables and dependent variables. Logistic regression analysis used CVD as a dependent variable. Receiver operating characteristic (ROC) curves were generated for the RDW using the CVD as a reference. P<0.05 was considered significant.

RESULTS AND DISCUSSION

The study population consisted of 160 patients (101 females/59 males). The mean age was 52.32 ± 10.83 years. 63 patients (39.4%) had mild OSAS, 39 (26.9%) had moderate OSAS, and 58 (58.3%) had severe OSAS. There were no differences in terms of age and sex among all the groups. CVD were significantly different among the groups (p=0.007). However, there were no significant differences among the groups with regard to diabetes mellitus, smoking, and BMI. Demographic and clinical characteristics, polygraphy findings and laboratory variables of the study population stratified by OSAS severity are shown respectively in Tables 1-3. RDW was significantly different among the groups. In fact, RDW in severe OSAS group was significantly higher than in mild (p<0.0001) and moderate OSAS group (p=0.021). A significant difference in term of RDW was also found between mild and moderate OSAS patients (p=0.034).

Variables	Mild OSAS group (n=63)	Moderate OSAS group (n=39)	Severe OSAS group (n=58)	p-value
Age (years)	50.92 ± 11.45	53.3 ± 13.28	53.18 ± 7.97	0.420
Sex (Males/ Females)	18/45	15/24	26/32	0.175
BMI (kg/m^2)	30.11 ± 5.27	32.02 ± 6.18	32.53 ± 5.75	0.094
CVD: n (%)	14 (20.96)	17 (25.8)	28 (45.16)	0.007
Hyperlipidemia: n (%)	11 (29.72%)	8 (18.91)	16 (43.24)	0.39
Diabetes mellitus: n (%)	13 (5.29)	8 (23.52)	12 (35.29)	0.99
Smoking: n (%)	10 (20)	10 (27.5)	17 (42.5)	0.197

Table 1: Demographic and clinical characteristics of the study group.

Variables	Mild OSAS group (n=63)	Moderate OSAS group (n=39)	Severe OSAS group (n=58)	p-value
AHI	8.64 ± .09	20.2 ± 4.3	48.56 ± 18.17	<0.001

Lowest saturation (%)	81.68 ± 10.09	81.5 ± 7.59	73.96 ± 9.48	<0.001
Desaturation index	8.28 ± 7.1	17.45 ± 8.24	43.07 ± 19.72	<0.001

Table 2: Polygraphy findings of the study group.

Variables	Mild OSAS group (n=63)	Moderate OSAS group (n=39)	Severe OSAS group (n=58)	p-value
RDW (%)	13.8 ± 1.13	14.33 ± 1.3	14.97 ± 1.33	<0.001
WBC (10^9/mm^3)	6,65 ± 1.55	6.58 ± 2.25	7.25 ± 1.71	0.12
Hb (g/dL)	13.2 ± 0.98	13.10 ± 1.02	13.38 ± 1.13	0.45
Plt (10^3/mm^3)	231.6 ± 51.85	251.78 ± 5.75	229.58 ± 66.72	0.185
CRP (mg/L)	5.08 ± 4,39	6.35 ± 3.54	8.54 ± 4.57	<0.001

Table 3: Laboratory variables of the study group.

All factors that can determinate CVD were evaluated by univariate analysis. Parameters associated with CVD were therefore introduced in a logistic regression analysis that included RDW, CRP, age, sex, tobacco consumption, hyperlipidemia, diabetes mellitus and BMI. The independent predictors of CVD in OSAS were RDW, CRP and age (Table 4).

Variables	p-value	Odds ratio	95% CI
Sex	0.93	1.058	0.258-4.338
Age (years)	0.013	1.085	1.017-1.157
BMI (kg/m^2)	0.081	1.11	0.987-1.249
Smoking	0.598	0.632	0.115-3.476
Diabetes mellitus	0.633	1.386	0.363-5.29
Hyperlipidemia	0.711	1.282	0.344-4.779
RDW (%)	<0.001	3.095	1.69-5.66
CRP (mg/L)	0.046	1.136	1.002-1.287

Table 4: Risk factors for cardiovascular diseases in patients with obstructive sleep apnea syndrome.

Using the receiver operator curve analysis, the best RDW to find patients with CVD in OSA was calculated. The area under curve (AUC) was 0.884 (95% confidence interval 0.834-0.934, p<0.001). The cut-off level for RDW with optimal sensitivity and specificity was calculated as 14.45 with sensitivity of 81% and specificity of 75%. Furthermore, the calculated AUC for the RDW was higher than the AUC for the CRP which was 0.783 (95% confidence interval 0.710-0.856, p<0.001). There are two main findings in the present study. First, RDW levels are significantly increased in a proportional manner as the severity of OSAS increased. Second, we found a significant association between high RDW levels and CVD in OSAS. The association remained significant even after allowing for multiple potential confounding factors. RDW is a routine measure of the size heterogeneity of circulating RBCs and is reported as a component of a complete blood count. The standard size of RBCs is about 6-8 μm, and the normal reference range of RDW for humans is 11% to 15%. RDW has been shown to be a strong independent predictor of morbidity and mortality in patients with chronic heart failure or newly diagnosed symptomatic heart failure and in patients with coronary artery disease. A high level of RDW is considered to indicate a change in the functions of the RBCs such as adhesion, ability to deformation and RBCs agglutinin release promoted by systemic inflammatory response and excessive oxidative stress. Therefore, blood flow dynamics are compromised and both coagulation and thrombosis are stimulated. The key point proposed in the association between RDW and CVD in OSAS has been the inflammation. Number of studies have shown that systemic inflammatory response due to recurrent intermittent hypoxia and sleep fragmentation in OSAS can inhibit, by inflammatory mediators, the differentiation and maturation of RBCs, thus increasing the RDW.

Indeed, Bergeron et al evoked the increase in markers of systemic inflammation in OSAS by describing the high production of IL-6 or TNF-α and the presence of a high plasma level of VEGF (vascular endothelial growth factor) and erythropoietin, a proof of an adaptive response to IH through stimulation of erythrocyte production and neovascularization. One of the potential links between RDW and CVD in OSAS would be the ineffective erythropoiesis desensitizing bone marrow erythroid progenitors to erythropoiesis which inhibits RBCs maturation and promotes anisocytosis. Release of nonmature RBCs into the blood circulation would change the laminar flow and accelerate deposition of the RBCs at the vessel wall causing, therefore, luminal stenosis or blockage.

Most of studies, while studying the usefulness of RDW in OSAS, excluded patients with CVD. Sökücü, et al. evaluated the value of RDW in predicting the severity of OSAS and found a positive correlation between RDW and AHI, with an AHI significantly higher in in the group of patients with high RDW (>15). Liu, et al. also demonstrated a positive correlation between RDW and AHI. However, Oszu, et al. investigated the correlation of the RDW level not only with the severity of OSAS but also with cardiovascular events and concluded that RDW ≥ 13.6% was found to be associated with high risk for CVD in patients with OSAS. In addition to metabolic dysregulation , oxidative stress, activation of the sympathetic nervous system and platelet activation, altered blood flow dynamics reflected by a high level of RDW has been revealed one of the numerous mechanisms leading to CVD in OSAS patients. Although our study is retrospective and a single-center study with a small

patient group, it brings an important contribution by evaluating the cut-off level of RDW for CVD in the patients with OSAS which was found to be 14.45.

This value may be taken into account in daily practice in sleep laboratories. These findings are all the more important when looking at AUC. The RDW achieved the greatest AUC as a predictor of CVD better than CRP which was shown by previous studies as a strong predictor of cardiovascular risk. OSAS is not a simple abnormality of the upper airways. It is a disease with multiple systemic consequences in particular consequences in the cardiovascular area (pulmonary hypertension, resistant systemic hypertension, chronic heart failure, arrhythmia, myocardial infarction and stroke), increasing mortality, and affecting familial, professional and social life. Therefore, managing CVD leads to improve the quality of life of OSAS patients.

CONCLUSION

The findings of this study suggest that there is an association between high RDW levels and cardiovascular events in patients with OSAS. Therefore, RDW, a simple, relatively inexpensive, and universally available marker could have the ability to predict CVD in OSAS. To better clarify that issue, further prospective studies are warranted.

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