NEW RESEARCH

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Can Red Blood Cell Distribution Width Predict Severity of Obstructive Sleep Apnea Syndrome?

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SCIENTIFIC INVESTIGATIONS

Study Objectives: Red blood cell distribution width (RDW) is a newly recognized risk marker for various diseases. We evaluated the value of RDW in predicting the severity of obstructive sleep apnea syndrome (OSAS).

Methods: From retrospective analyses of 526 patients admitted to our sleep laboratory for polysomnography between January 2010 and July 2011, 108 patients with complete medical records and hemogram analyses were evaluated.

Results: The study population consisted of 108 patients (age: 49.16 ± 11.1 [range 16-76] years; 72 [66.7%] males). In the overall population, the mean RDW was 14.04 (± 2.37), and 31 patients (28.7%) had RDW > 15. RDW increased significantly with increased severity of OSAS (p = 0.046) and was positively correlated with the apnea-hypopnea index (p = 0.002, r = 0.300), even in the non-anemic group (p = 0.013, r = 0.291). The apnea-hypopnea index was significantly higher in the group with high RDW (> 15; p = 0.046). RDW was negatively correlated with sleep time (p = 0.028, r = 0.217), average oxygen saturation of hemoglobin (p = 0.003, r = -0.239), and minimum desaturation value (p = 0.016, r = -0.235).

Conclusions: In patients referred with a clinical diagnosis of OSAS, RDW may be a marker for the severity of the condition. As RDW is usually included in a complete blood count, it could provide an inexpensive tool for triaging OSAS patients for polysomnography evaluation.

Keywords: Apnea-hypopnea index, red blood cell distribution width, obstructive sleep apnea syndrome, hemogram

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Obstructive sleep apnea syndrome (OSAS) is characterized by collapse of the upper airway during sleep, recurring apnea, intermittent hypoxemia, and daytime sleepiness. The severity of OSAS is estimated by the number of apnea/hypopnea episodes per hour of sleep and is expressed as the apnea-hypopnea index (AHI). Based on the AHI, OSAS can be classified as mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI > 30).[1]

OSAS and cardiovascular diseases are closely related. Obstructive sleep apnea is a highly prevalent sleep disorder and leads to cardiovascular complications. The association between OSAS and cardiovascular disease arises from their overlapping risk factors, including obesity, a sedentary lifestyle, male gender, and older age.[2]

Red blood cell distribution width (RDW) is a numerical measure of the size variability of circulating erythrocytes and is routinely reported as a component of a complete blood count in the differential diagnosis of anemia. The standard size of RBCs is about 6-8 μm, and the normal reference range for human red blood cells is 11% to 15%.[3,4] Disorders related to ineffective erythropoiesis or increased red blood cell destruction cause greater heterogeneity in size and thus a higher RDW.[4,5] Recently, RDW has been reported as a strong independent predictor of adverse outcomes in the general population and is believed to be associated with cardiovascular morbidity and mortality in patients with a previous myocardial infarction.[6-8]

Considering the association between OSAS and cardiovascular disease and the overlapping risk factors, we evaluated RDW as a severity index in OSAS and the relationship of RDW with the AHI and other sleep parameters.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Diagnosis and severity of obstructive sleep apnea hypopnea syndrome (OSAS) is determined using apnea hypopnea index form a single night polysomnography. Accurate assignment of severity is important to establish early treatment. However there is a long waiting list for this test in many centers and evaluation with Epworth Sleep Scale is not good enough to predict severity of the disease. So new indices is needed to decide for whom the test needs priority.

Study Impact: In this current study, red cell distribution width was showed to be related to OSAS severity. It is a part of complete blood count and can be used to decide for whom we should give earlier appointment.

METHODS

Patients

This study was designed as a retrospective analysis of a cross-sectional cohort and was approved by the institutional ethics committee. The overall study population consisted of 526 patients who were admitted to the sleep laboratory of our hospital with complaints of snoring, witnessed apnea, or daily sleepiness, and in whom polysomnography (PSG) had been performed between January 2010 and July 2011.

Table 1—Properties of the study cases

Parameters		
Sex	72 male/36 female	66.7%/32.3%
Age (y)	49.16 ± 11.1	16-76
Anemia	15 anemic/93 nonanemic	13.9%/86.1%
Recording time (min)	451.1 ± 38.0	269-507
Sleep time (min)	353.6 ± 70.6	127-485
Average saturation (%)	91.4 ± 6.6	63-98

Table 2—RDW values by OSAS classification of the study cases

AHI	Severity classification	Number of patients	Ratio	RDW (mean ± SD)
5-15	Mild	16	14.8%	13.15 ± 1.7
15-30	Moderate	19	26.9%	13.10 ± 2.3
> 30	Severe	63	58.3%	14.67 ± 2.5

Demographic and health behavior-related data, including age, gender, body mass index (BMI), and age-associated medical conditions, as well as medical histories regarding sleep habits and cardiovascular disease were collected from patient records. A respiratory function test, posteroanterior chest x-ray, and electrocardiography performed before PSG were evaluated, and complete blood counts were analysed. Patients known to have cardiovascular, renal, or hepatic diseases were excluded. Patients diagnosed with obesity hypoventilation, overlap syndrome, complex sleep apnea, central sleep apnea, Cheyne-Stokes sleeping disorder, or REM-induced OSAS were excluded from the PSG results. These patients were excluded because these diseases have comorbidities that could cause inflammation, such as morbid obesity, COPD, cardiovascular disease. Also in REM-induced OSAS there are other severity criteria other than AHI. According to these criteria, of 526 consecutive patients, 108 met inclusion criteria and had medical records that included a complete blood count performed in the morning were included and analysed.

Based on the AHI, patients were grouped into three OSAS severity categories: mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI > 30). None of the patients had an AHI ≤ 4. Patients were also grouped by BMI, according to the WHO classification: < 20, 20-24.9, 25-29.9, 30-34.9, 35-44.9, 45-49.9, and > 50. Anemia was diagnosed as a hemoglobin value < 13 in men and < 12 in women.

Measurement of RDW and Laboratory Parameters

Morning blood samples were drawn from participating patients after an overnight fast > 12 h, and analyzed. RDW, hemoglobin level, white blood cell count, and mean corpuscular volume (MCV) were determined using an ABX Pentra 120 analyzer, with a differential count included as part of the complete blood cell count.

Polysomnography

Overnight polysomnography was performed using an Embla A-10 data acquisition and analysis system (Medcare Flaga, Reykjavik, Iceland) in the attended setting at a sleep laboratory under baseline conditions. The following physiological parameters were monitored: brain electrical activity by electroencephalography (EEG; with electrode placements at C4-A1, C3-A2, O2-A1, and O1-A2); eye movements by electro-oculography (EOG); submental muscle activity by electromyography (EMG); ribcage and abdominal effort by respiratory inductive plethysmography (RIP; XactTrace, Medcare Flaga); body position, by a calibrated sensor; snoring sounds by a piezoelectric sensor; oronasal flow, by a nasal pressure cannula (Medcare Flaga); oxygen saturation of hemoglobin (SpO_2) by pulse oximetry (8000J; Nonin Medical, Plymouth, MN, USA) with the averaging time set at 3 s; and electrical activity of the heart by electrocardiography (ECG; lead II) sampled at 512 Hz. Sleep stages and arousals were scored according to standard criteria by a skilled pulmonary physician (LK) using the Somnologica Studio software package (Medcare Flaga). Apnea was defined as a cessation of airflow ≥ 10 s and was classified as obstructive in the presence of continued movement on RIP or central in the absence of movement on RIP. Hypopnea was defined as a reduction ≥ 50% in oronasal flow amplitude ≥ 10 s, accompanied by ≥ 3% desaturation and/or arousal. Hypopnea was classified as obstructive when there was evidence of upper airway resistance, such as snoring, paradoxical motion in the respiratory bands, or inspiratory flow limitation indicated by nasal pressure signals.

Statistical Analysis

All variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Continuous variables with normal distributions are expressed as mean ± standard deviation (SD). Continuous variables with non-normal distributions are summarized as medians (interquartile range, IQR). Categorical variables are expressed as numbers (percentage). RDW was normally distributed, and comparisons between independent groups were made using the Mann-Whitney *U* test. Correlations between RDW and nonparametric variables were analysed using Spearman correlation. Correlations between RDW and parametric variables were analysed using Pearson correlation. ANOVA was used for comparisons.

RESULTS

The study population consisted of 108 patients (mean age: 49.16 ± 11.1 [range 16-76] years; 72 (66.7%) males). Most patients (92.6%) were under 65 years of age. Fifteen patients (13.9%) were anemic.

Mean recording time was 451.1 ± 38.0 (269-507) min, with a mean sleep time of 353.6 ± 70.6 (127-485) min. Mean average oxygen saturation during sleep was 91.4% ± 6.6% (63%-98%) (**Table 1**).

In the overall population, the mean RDW was 14.04 (± 2.37), and 31 patients (28.7%) had an RDW > 15. Sixteen patients (14.8%) had mild OSAS, 19 (26.9%) had moderate OSAS, and 63 (58.3%) had severe OSAS. Mean RDW values in each group are shown in **Table 2**.

RDW was not correlated with age or gender. Among other hematological variables, RDW showed an inverse correlation

with MCV (86.4 [31.7-108] fL; p = 0.022, r = −0.221). RDW was also correlated with platelet number (p = 0.013, r = 0.239).

Polysomnographic Parameters

Platelet number, BMI, AHI, and oxygen desaturation index (ODI) were positively correlated with RDW; whereas MCV, average oxygen saturation of hemoglobin (average SpO_2), minimum oxygen saturation of hemoglobin (minimum SpO_2), and sleep time were negatively correlated with RDW. After correction for anemia, RDW was still positively correlated with AHI and ODI and negatively correlated with average SpO_2, minimum SpO_2, and sleep time. Correlations between RDW and the sleep parameters are shown in **Table 3**.

The AHI was significantly higher in the group with high RDW values (> 15; p = 0.046). Significant positive relationships between RDW and hemoglobin, MCV, platelet count, and AHI were seen in the groups with normal RDW and high RDW values (**Table 4**, **Figure 1**).

Based on one-way ANOVA after corrections, RDW increased significantly as the severity of OSAS increased (p = 0.046). The relationships between mild OSAS and moderate OSAS, mild OSAS and severe OSAS, and moderate OSAS and severe OSAS were p = 0.812, p = 0.005, and p = 0.006, respectively (**Figure 2**).

DISCUSSION

This retrospective study is one of only a few studies examining the relationship between RDW and AHI in OSAS. Although preliminary, the results support a correlation between RDW and the severity of OSAS.

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.[5,6] In addition, RDW has been a strong predictor of all-cause mortality in population cohorts.[6,7] RDW was not only associated with cardiovascular disease, but also predicted mortality from acute pulmonary embolism and community-acquired pneumonia.[9,10] These findings suggest that the pathophysiology leading to increased RDW may affect the outcomes in chronically ill patients, regardless of anemia status.

Chronic inflammation is also present in OSAS patients, as a part of this multisystem disease. There is evidence that inflammatory processes leading to endothelial dysfunction play a pivotal role in the pathogenesis of cardiovascular complications in OSAS. Various studies have demonstrated elevated

Table 3—Correlations of RDW with other parameters

	All patients		Non-anemic	
Parameters	**r value**	**p value**	**r value**	**p value**
WBC ($10^3/mm^3$)	0.015	0.878	0.040	0.702
Hb (g/dL)	-0.062	0.526	0.242	0.020
Plt ($10^3/mm^3$)	0.239	0.013*	0.146	0.163
MCV(μm³)	-0.221	0.022*	-0.057	0.585
Age (years)	0.066	0.496	0.085	0.417
BMI	0.213	0.030*	0.298	0.005*
Recording time (min)	-0.064	0.509	-0.086	0.412
Sleep time (min)	-0.217	0.028*	-0.213	0.044*
REM duration (min)	0.013	0.895	0.072	0.502
AHI	0.300	0.002*	0.291	0.013*
Average SpO_2 (%)	-0.239	0.013*	-0.295	0.004*
ODI	0.295	0.008*	0.352	0.003*
Minimum SpO_2 (%)	-0.235	0.016*	-0.321	0.002*

BMI, weight/height²; AHI, apnea hypopnea index; ODI, oxygen desaturation ındex; *p < 0.05.

Table 4—Evaluation of parameters between groups with normal RDW and higher RDW

Parameters	**RDW < 15 (n = 77)**	**RDW ≥ 15 (n = 31)**	**p value**
Age (years)	49.27 ± 11.61	48.90 ± 9.91	NS
Sex	51 male (66.23%)	21 male (67.74%)	NS
WBC ($10^3/mm^3$)	7.57 ± 2.03	7.60 ± 1.86	NS
RBC ($10^3/mm^3$)	4.86 ± 0.52	4.94 ± 0.83	NS
Hb (g/dL)	14.45 ± 1.47	13.54 ± 2.59	0.023
MCV (μm³)	87.94 ± 8.25	82.54 ± 6.23	0.001
Plt ($10^3/mm^3$)	237.07 ± 61.47	284.61 ± 70.00	0.001
BMI	31.70 ± 6.48	32.14 ± 7.85	NS
Recording time (min)	450.58 ± 41.28	452.25 ± 28.61	NS
Sleep time (min)	358.78 ± 67.28	341.07 ± 78.04	NS
REM duration (min)	18.30 (12.6-25.8)	17.70 (12.8-30.6)	NS
AHI	33.3 (21.0-57.2)	58 (32.5-71.4)	0.046
OSAS classification	Mild:13 Moderate:25 Severe:39	Mild:3 Moderate:4 Severe:24	0.030
Average SpO_2 (%)	91.87 ± 6.38	90.34 ± 7.26	NS
ODI	10 (4-32)	25 (8.3-63.7)	NS
Minimum SpO_2 (%)	77.53 ± 14.61	74.38 ± 15.66	NS

p > 0.05 were nonsignificant (NS); BMI, weight/height²; AHI, apnea hypopnea index; SpO_2, oxygen saturation of hemoglobin measured by pulse oximeter; ODI, oxygen desaturation index; n, number of patients.

Figure 1—Correlations graphic of RDW levels with AHI

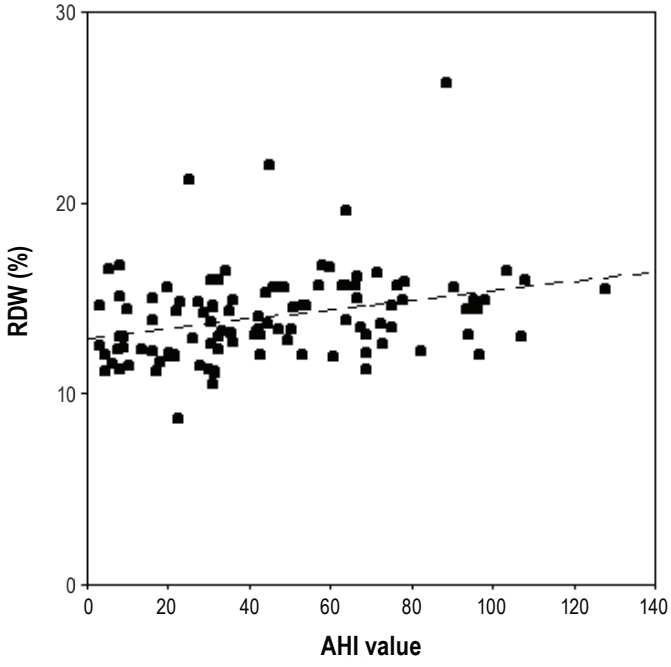
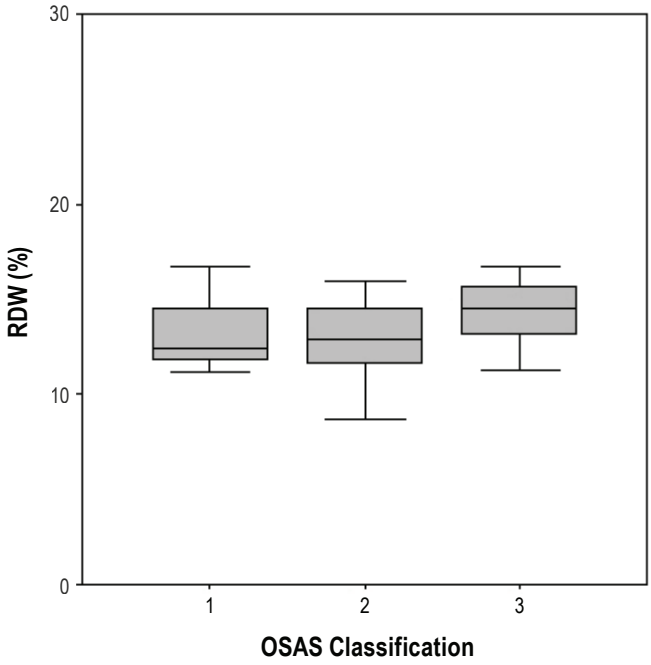


Figure 2—Graphic drawn in between OSAS classification and RDW value



OSAS classifications as 1 = AHI between 5-15; 2 = AHI between 15-30; 3 = AHI > 30.

inflammatory marker levels in OSAS patients compared with matched controls, with a significant fall after effective treatment with continuous positive airway pressure.[11] In addition to inflammation, intermittent hypoxia and sleep deprivation may also explain the relationship between RDW and AHI in OSAS. Intermittent hypoxia in OSAS results in the activation of pro-inflammatory transcription factors, which promote the activation of various inflammatory cells, particularly lymphocytes and monocytes.[12] Thus, hypoxia also triggers inflammation in OSAS patients.

Our results revealed a positive association between RDW and AHI. This relationship was previously reported in a study involving a small number of patients.[13] However, in contrast to that study, our study found that the relationship remained after adjusting for anaemia, an important confounding factor. Our finding is consistent with previous reports suggesting that the inflammatory mechanism in OSAS may not be directly linked to hemoglobin levels, as RDW was only modestly correlated with serum hemoglobin.[8] Thus, our study demonstrates a relationship between severity of OSAS and RDW that is dependent on inflammation and intermittent hypoxia and independent of anemia.

We also found a negative association of RDW with average and minimum oxygen saturation during sleep, which could be explained by the effect of hypoxia on RDW. Intermittent hypoxia is a major trigger for the cardiovascular and metabolic alterations associated with OSAS.[12,14] Recurrent pharyngeal collapse during sleep can lead to repetitive sequences of hypoxia-reoxygenation, which induce immuno-inflammatory alterations and cardiovascular complications.[12,14] A positive relationship between RDW and the oxygen desaturation index may also indicate the severity of OSAS. On the other hand, we found only a weak negative correlation between sleep time and RDW, although effects of sleep deprivation and shorter sleep duration on metabolic processes have been reported.[15,16]

One of the weaknesses of our study is that because it is a retrospective study, we do not have markers of inflammation which could affect RDW values, thus we could not evaluate their correlation. Also, although RDW could not be used as a screening tool for general population depending on this study results because it could be affected by various independent variables, it could be used in sleep laboratories with long waiting lists to give earlier appointment so these patients could able to reach earlier treatment options.

In conclusion, the present study demonstrated a positive relationship between RDW at presentation and the AHI in patients evaluated for OSAS, even in non-anemic patients. The study of anisocytosis may provide important pathophysiological insights into OSAS. The retrospective evidence of an association between elevated RDW and the severity of OSAS in the present study suggests the clinical usefulness of RDW values. As RDW is usually included in a complete blood count, it could provide an inexpensive tool for triaging OSAS patients for polysomnography evaluation. Patients with severe OSAS could be identified based on RDW at the first examination and given priority for testing and treatment. Prospective studies with larger populations, using different severity criteria and excluding other inflammatory causes, are needed to confirm RDW as a useful severity assessment tool in OSAS.

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