

Evaluation of the predictive value of red blood cell distribution width for onset of cerebral infarction in the patients with obstructive sleep apnea hypopnea syndrome

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Abstract

Red blood cell distribution width (RDW) is a risk factor for the complications caused by obstructive sleep apnea hypopnea syndrome (OSAHS). This study was aimed to evaluate the predictive value of RDW for the occurrence of cerebral infarction in patients with OSAHS.

We conducted a prospective study of 129 consecutive patients who were admitted to the Sleep Laboratory of in the Tenth People's Hospital of Shanghai (China) with complaints of snoring, apnea, or daytime sleepiness. All patients underwent polysomnography between June 2011 and May 2012. In total, 90 patients met the study criteria and were included in the study; there are 71 men and 19 women.

RDW correlated positively with the apnea hypopnea index (AHI) ($P = .00$, $r = 0.76$). Logistic regression analysis showed correlations between each variation and cerebral infarction, high blood pressure (odds ratio [OR] = 4.72, $P = .220$), diabetes (OR = 2.67, $P = .490$), hyperlipidemia (OR = 7.42, $P = .190$), RDW (OR = 58.24, $P = .020$), and AHI (OR = 243.92, $P = .001$). RDW $\geq 15\%$ showed a higher predictive value for the occurrence of cerebral infarction in patients with OSAHS (area under curve 0.837; sensitivity 0.919; specificity 0.755), with positive and negative predictive values of 0.697 and 0.938, respectively.

RDW correlates positively with AHI. RDW values $\geq 15\%$ are predictive for the occurrence of cerebral infarction in patients with OSAHS.

Abbreviations: AHI = apnea hypopnea index, BMI = body mass index, EEG = electroencephalogram, EPO = erythropoietin, MRI = magnetic resonance imaging, OSA = obstructive sleep apnea, OSAHS = obstructive sleep apnea hypopnea syndrome, PSG = polysomnography, RBC = red blood cell, RDW = red blood cell distribution width, RIP = respiratory inductive plethysmography, ROS = reactive oxygen species.

Keywords: cerebral infarction, erythrocyte index, obstructive, polysomnography, sleep apnea syndromes

1. Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a sleep-related breathing disorder with complex etiology and a prevalence in China of between 3.62% and 4.78%. The pathogenesis of this potentially lethal disorder involves narrowing and obstruction of the upper airways accompanied by disruption of central nervous regulation of respiration.^[1] In

2011, the American Heart and Stroke Association classified sleep-disordered breathing as the primary risk factor for stroke,^[2] indicating the importance of OSAHS in terms of human health and the national economy.^[3] Consequently, a predictive indicator of the severity of OSAHS and its relationship with cerebral infarction is urgently required. The present study was designed to find a predictive marker for complications of sleep apnea hypopnea syndrome (OSAHS), and red blood cell distribution width (RDW) may be a useful predictor of cerebral infarction in patients with sleep apnea syndrome. RDW is an index of red blood cell (RBC) heterogeneity, with values correlating directly with RBC volume. Blood flow dynamics are altered by disparity between the sizes of RBCs^[4]; therefore, RDW is regarded as a new type of cardiocerebral vascular risk marker, with a high RDW predictive of severe OSAHS.^[5] The current study showed that the increased RDW was an independent risk factor for the prognosis of patients with acute cerebral infarction.^[6] Increased RDW reflects a potential inflammatory reaction and excessive oxidative stress, which is mainly caused by disruption of the RBC membrane. This not only increases the osmotic fragility of RBCs, but also changes functions, such as adhesion, deformation ability, increased RBC agglutinin release. These changes in turn increase blood flow resistance, and promote coagulation and thrombus formation.^[7,8]

Editor: Ahmet Emre Eskazan.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:29(e7320)

Received: 22 December 2016 / Received in final form: 24 May 2017 / Accepted: 29 May 2017

<http://dx.doi.org/10.1097/MD.0000000000007320>

2. Materials and methods

2.1. Study design

This prospective study consisted of 129 consecutive patients who were admitted to the Sleep Laboratory of in the Tenth People's Hospital of Shanghai (China) with complaints of snoring, apnea, or daytime sleepiness. All patients underwent polysomnography (PSG) between June 2011 and May 2012. The study protocol was approved by the local ethics committee and all patients gave written informed consent.

Demographic and health behavior-related data, including details of age, sex, body mass index (BMI), Epworth sleepiness scale scores, and medical histories regarding sleep habits, were collected from patient records. A physical examination, respiratory function test, posteroanterior chest X-ray, and electrocardiography performed before PSG were evaluated, and complete blood counts were analyzed. Magnetic resonance imaging (MRI) of the brain was performed.

2.2. Participants

The inclusion criteria were as follows: symptoms of nocturnal snoring and/or excessive daytime sleepiness and an apnea hypopnea index (AHI) $\geq 5/h$ in the PSG evaluation; age range 18 to 75 years old. The exclusion criteria were as follows: any known cardiac disease, lung disease, diabetes (defined as fasting plasma glucose >126 mg/dL and/or antidiabetic treatment); chronic renal or hepatic diseases (because chronic disease usually affects RDW); use of acetylsalicylic acid or other anticoagulant therapy during the previous week; hemoglobin <12 mg/dL (to exclude anemia); central sleep apnea syndrome diagnosed in the PSG evaluation, and previous treatment for obstructive sleep apnea, cognitive dysfunction, cancer, long-term alcohol abuse, and poor patient compliance. All subjects meeting the inclusion criteria were enrolled consecutively in this study conducted at the Shanghai Tenth People's Hospital (China). All patients underwent MRI of the brain before the study and after 2 years of follow-up. The lesion site and number of each patient was recorded and compared to identify new cerebral infarction lesions. The results were evaluated by a neurology physician and a radiologist and cases of dispute were resolved by the director of the MRI facility. Patients were grouped according to the occurrence of a new cerebral infarction after 2 years of follow-up, and then subdivided into cerebral infarction and noncerebral infarction groups.

2.3. Measurement of laboratory parameters

Complete blood counts and blood coagulation tests were performed in all the study groups on day 1 after the PSG evaluation and after the 2 years of follow-up. Participants with normal AHI were not required to follow-up. Venous blood samples were drawn from participants between 07:00 and 08:00 after an overnight fast (>8 h) and analyzed within 1 h. The RDW, MPV, PDW, mean corpuscular volume (MCV), and platelet count were determined using a Beckman Coulter automatic flow cytometry LH750/LH755; (California, America) a differential count was included as part of the complete blood cell count. D-dimer and fibrinogen levels were determined using a coagulation analyzer HF6000-4 (Shandong Province, China). Determination of the amount of C-reactive protein levels was determined using an automated C-reactive protein analyzer QR-1000 (Shanghai, China).

2.4. Polysomnography

All subjects underwent an PSG with a portable polysomnographic SOMNolab2 (Weinmann Brand, Hamburg, Germany)

using a standard montage of electroencephalogram (EEG), electro-oculogram, electromyogram, and electrocardiogram signals together with pulse oximetry and airflow, detected using combined oronasal thermistors. Thoracic cage and abdominal motion were recorded by respiratory inductive plethysmography (RIP) (Weinmann). PSG was conducted between 22:00 and 07:00 hours. Apneas, hypopneas, and EEG recordings were scored manually according to standard criteria. 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 for >10 s, accompanied by $>3\%$ desaturation and/or arousal.

2.5. MRI examination

Cerebral infarction was diagnosed by nuclear MRI (Model: 1.5T superconducting MRI, GE, Fairfield, Connecticut, America) using T₂-FLAIR sequences. Lacunar infarction was diagnosed on the basis of penetration of arterial lesions <15 mm in diameter. FLAIR imaging parameters were head quadrature coil. T₂-FLAIR: axial; thickness 5 mm; interval 2 mm; matrix 256 \times 224. Display range for 220 cm \times 220 cm, Repetition time = 8802 ms, Echo time = 129 ms, Inversion time = 2200 ms, and number of signal acquisition for 1. Eight regions (basal ganglia, frontal lobe, thalamus, temporal lobe, parietal lobe, occipital lobe, brainstem, and cerebellum) were evaluated to identify the subtypes of cerebral infarction.

2.6. Follow-up

All subjects were followed-up at 6-month intervals, when patients recorded incidences of dizziness, headache, chest tightness, and chest pain. Details of blood pressure, lipid, and glucose control were compared with the data from the previous follow-up; no major fluctuations in these 3 indicators were observed in any of the subjects. One patient complained of occasional dizziness (1 episode) at the second follow-up; spontaneous remission occurred without any special treatment and no recurrence was reported. In cases of acute dizziness, headache, chest pain, chest tightness during the 2-year follow-up, participants were withdrawn from the follow-up and received timely medical treatment.

2.7. Statistical analysis

Data were analyzed with SPSS17.0 English version (SPSS Software, IBM, New York, America). All variables were tested for normality of the distribution using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as means \pm standard deviation. Categorical variables were expressed as numbers (percentages). Correlations between nonparametric variables were analyzed using Spearman correlation. Correlations between parametric variables were analyzed using Pearson correlation. Comparisons between independent groups for the values that were normally distributed were conducted using Student *t* test and between values not normally distributed using the Mann-Whitney *U* test. A logistic regression analysis model was used to compare the correlation between independent variables and dependent variables. Receiver operating characteristic curves were used to analyze the predictive value of variables.

3. Results

A total of 129 consecutive patients were enrolled in this study. Of these, 26 patients were AHI $<5/h$ and 103 were OSAHS. The 13 excluded patients comprised 1 case of cholestasis liver cirrhosis, 2

Table 1
Characteristics of the study cases.

Parameters	AHI	Number of patients	RDW (%), mean ± SD
Mild	5–15	25	13.03 ± 0.54
Moderate	15–30	31	14.89 ± 0.86
Severe	>30	34	15.62 ± 0.83

AHI = apnea hypopnea index, RDW = red cell distribution width, SD = standard deviation.

cases of chronic glomerulonephritis, 1 case of acute pneumonia, 2 cases of long-term alcoholic abuse, 4 cases with a history of chronic obstructive pulmonary disease, and 3 cases of noncompliance; 90 patients met the inclusion criteria, but they all refused to accept ventilator treatment for economic reasons or other reasons, they were willing to join the study, they wanted to see what happens without the use of noninvasive ventilation, doctors had repeatedly told them the complications of OSAHS on humans.

In the overall study subjects, 25 patients (27.8%) had mild OSAHS, 31 (34.4%) had moderate OSAHS, and 34 (38.8%) had severe OSAHS. The general characteristics of the study participants and the mean RDW values in each group are shown in Table 1. RDW was not correlated with age or sex. Among other hematological variables, RDW showed an inverse correlation with MCV ($P = .040$, $r = -0.706$). RDW correlated most closely with AHI ($P = .002$, $r = 0.820$), as shown in Fig. 1 and Table 2. Platelet number, fibrinogen, D-dimer, BMI, and WBC counts correlated positively with RDW ($P < .05$). Correlations between RDW and other parameters are shown in Table 2. Among the patients with OSAHS after 2 years of follow-up, new cerebral infarctions occurred in 37 patients at the last follow-up, while 53 were without new cerebral infarctions. The cases of cerebral infarctions comprised 2 cases of nonlacunar infarction (1 case of moderate OSAHS and 1 case of severe OSAHS) and 35 cases of lacunar cerebral infarction (9 cases of moderate OSAHS and 26 cases of severe OSAHS). We gave free treatment to patients with new cerebral infarction. AHI and RDW were significantly higher in the group with new cerebral infarction foci ($P = .001$ and $P = .001$, respectively). As shown in Table 3, significant differences were observed between the groups with

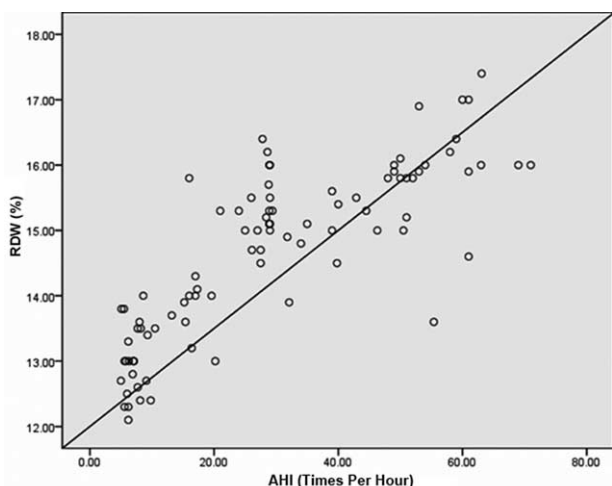


Figure 1. Correlations of red blood cell distribution width levels with apnea hypopnea index.

Table 2
Correlations of RDW with other parameters.

Parameters	r	P
Sex	0.110	.197
Age, y	0.144	.176
BMI, kg/m ²	0.392	.010*
Fibrinogen, g/L	0.501	.005*
D-dimer, mg/L	0.662	.004*
Platelets, ×10 ⁹ /L	0.739	.030*
MCV, fl	-0.706	.040*
WBC, ×10 ⁹ /L	0.594	.020*
AHI	0.820	.002*

AHI = apnea hypopnea index, BMI = weight/height², RDW = red blood cell distribution width, WBC = white blood cell.

* $P < .05$.

and without new cerebral infarctions in terms of BMI, platelet count, fibrinogen and D-dimer, prevalence of hypertension, except age, prevalence of diabetes mellitus, and prevalence of hyperlipidemia. All of these were implicated as risk factors for the incidence of cerebral infarction. To determine those that were significantly related with RDW, we performed a logistic regression analysis of the correlation between risk factors and cerebral infarction. As shown in Table 4, AHI and RDW were significantly correlated with cerebral infarction ($P < .05$). The predictive value of RDW for cerebral infarction was found to be greater than that of other risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia (Table 5).

Table 3
Comparison of parameters between groups with and without infarction.

Parameters	Infarction (n=37)	No infarction (n=53)	t	P
Age, y	56.00 ± 8.12	55.32 ± 9.12		.69
BMI, kg/m ²	28.57 ± 2.75	26.99 ± 1.90	2.59	.01*
Fibrinogen, g/L	3.91 ± 0.66	3.35 ± 0.71	2.61	.01*
D-dimer, mg/L	2.96 ± 0.55	2.16 ± 0.98	2.85	.005*
Platelets, ×10 ⁹ /L	305.46 ± 18.94	235.11 ± 51.79		.005*
RDW, %	15.70 ± 0.73	13.93 ± 1.11	9.08	.001*
AHI	48.37 ± 12.09	16.42 ± 9.65		.001*
Hypertension	24/37	24/53		.008*
Diabetes	14/37	19/53		.85
Hyperlipidemia	22/37	37/53		.14

AHI = apnea hypopnea index, BMI = weight/height², n = number of patients, RDW = red cell distribution width.

* $P < .05$.

Table 4
Logistic regression analysis of correlations between RDW and other risk factors and cerebral infarction.

Risk factors	OR	P
Hypertension	4.720	.218
Diabetes	2.671	.491
Hyperlipidemia	7.423	.186
Fibrinogen	2.006	.589
D-dimer	7.796	.277
Platelet	4.370	.231
RDW	58.235	.023*
AHI	243.917	.001*

AHI = apnea hypopnea index, OR = odds ratio, RDW = red cell distribution width.

* $P < .05$.

Table 5**Comparison of predictive value of RDW and other traditional cerebral infarction risk factors.**

Risk factors	AUC	Sensitivity	Specificity	PPV	NPV
Hypertension	0.588	0.649	0.528	0.457	0.710
Diabetes	0.448	0.378	0.642	0.393	0.627
Hyperlipidemia	0.510	0.595	0.302	0.343	0.549
RDW	0.837	0.919	0.755	0.697	0.938

NPV=negative predictive value, PPV=positive predictive value, RDW=red cell distribution width (RDW cut-off value, 15%).

4. Discussion

In this prospective study of the correlation between RDW and AHI, we found that elevated RDW correlates significantly with cerebral infarction complications in patients with OSAHS. Current clinical research shows that conditions such as hemodynamic disorders, inflammation, blood hypercoagulability, and oxidative stress caused by OSAHS have a close relationship with the pathogenesis and prognosis of cardiovascular and cerebral disease.^[9–11] The main manifestations of OSAHS are apnea and hypopnea, with the existence of excessive oxidative stress, which is a simple mechanism underlying chronic inflammation in OSAHS.

Medical research has shown that the OSAHS-induced inflammatory response is systemic, and inflammatory factors can inhibit the differentiation and maturation of RBCs, thus increasing the RDW. The inflammatory factors IL-6, TNF- α , C-reactive protein, and IL-8 correlate significantly with elevated RDW. Furthermore, decreased IL-10 also correlates with increased RDW.^[12–14]

It is possible that high levels of inflammatory cytokines activate neutrophils or lymphocytes, and other aggressive cells, resulting in the RBC membrane damage and increased fragility. This causes pathological dissolution of RBCs and activation of the erythropoietin (EPO) gene, which increases RBC production in the bone marrow. However, excessive inflammation inhibits the differentiation of RBCs in each stage of maturation, leading to markedly increased RDW.^[15] Damaged RBCs are resistant to flow because of the loss of deformation capacity, and cannot pass through some small blood vessels, where RBCs with abnormal functional gather and cause thrombosis.

EPO promotes proliferation, differentiation, and maturation of stem cells to increase RBC numbers. Some studies have shown that EPO levels in patients with severe OSAHS are significantly higher at night than at any other time.^[16] In addition, increased EPO results in the generation of a large number of nonmature RBC. Release of these cells into the blood circulation changes the laminar flow, accelerating deposition of the RBCs at the vessel wall and causing luminal stenosis or blockage. Moreover, this process causes excessive oxidative stress due to the production of large amounts of reactive oxygen species (ROS). These ROS cause vascular endothelial damage, leading to the production of more ROS as part of the resulting inflammatory response; thus, a vicious circle is initiated.^[17] Sympathetic nervous system disorders, dysregulation of cerebral blood flow, endothelial cell injury, decreased RBC deformation ability, increased blood viscosity, and cell agglutination, as well as hemodynamic changes and other unknown factors cause OSAHS patients to be more prone to cerebral infarction.^[18]

This study confirmed the positive correlation of RDW with AHI, as well as the positive correlation between RDW and the

incidence of cerebral infarction. In addition, we found that the AHI exceeded 50 in the majority of patients with cerebral infarction. Infarction complications seriously affect the patient's cognitive function and other functions, leading to a reduction in the quality of life. It should be noted that the conclusions of this study are limited by the small sample size, and large-scale randomized-controlled clinical trials are required for further verification.

5. Conclusions

In summary, RDW is a new and convenient index of the severity of OSAHS with inflammatory reactions and the risk of cerebral infarction.

Acknowledgments

Thanks are due to Min Tan for assistance with the statistical aspects and to my tutor for valuable discussion.

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