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Research Article

Association between Hypoxia Parameters with White Matter Hyperintensity and Silent Cerebral Infarcts on Brain Magnetic Resonance Images in Patients with Obstructive Sleep Apnea

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Summary

Objective: This study evaluated the association between hypoxia parameters with white matter hyperintensity (WMH) and silent cerebral infarcts (SCI) on brain magnetic resonance (MR) images of patients with obstructive sleep apnea (OSA).
Methods: In this retrospective study, the study group was composed of 453 patients who were evaluated by overnight polysomnography (PSG). Data on hypoxia parameters, such as total sleep duration with oxygen saturation < 90% (ST_{90}), percentage of cumulative time with oxygen saturation < 90% (CT_{90}), and the lowest oxygen saturation (min SaO_2), were obtained from PSG. The presence of WMH and SCI was evaluated in all participants using brain MR images.
Results: Hypoxia parameters, such as ST_{90}, CT_{90}, and min SaO_2, were significantly associated with WMH ($P < 0.001$). The multiple regression analysis showed that CT_{90} was independently associated with SCI ($P = 0.038$). In addition, when participants were divided into two groups according to $CT_{90} < 10\%$ and $CT_{90} \geq 10\%$, age ($P = 0.002$), sex ($P = 0.015$), body mass index, Apnea-Hypopnea Index score, Epworth Sleepiness Scale score, and the presence of WMH, hypertension, and diabetes mellitus were significantly higher in the $CT_{90} \geq 10\%$ group compared with the $CT_{90} < 10\%$ group ($P < 0.001$ for all parameters). $CT_{90} \geq 10\%$ increased the risk of WMH 2.34-fold (95% confidence interval, 1.44–3.85; $P = 0.006$).
Conclusion: The severity of nocturnal intermittent hypoxia may contribute to the pathogenesis of WMH and SCI in patients with OSA.

Key words: Sleep apnea, snoring, oxygen saturation, hypoxia, stroke, magnetic resonance imaging

Obstrüktif Uyku Apnesi'nde Hypoksi Parametrelerinin Beyin MRG'de Saptanan Hiperintens Odak ve Sessiz Serebral İnfarkt ile İlişkisi

Özet

Amaç: Çalışmanın amacı obstruktif uyku apne sendrom'lu (OSA) olgularda hipoksi parametreleri ile beyin manyetik rezonans görüntülemede saptanan beyaz cevherde hiperintens odaklar (WMH) ve sessiz serebral infarkt (SCI) ile ilişkisini değerlendirmek.
Metod: Bu retrospektif çalışmada tüm gece polisomnografi yapılmış toplam 453 olgu alındı. Hipoksi parametreleri toplam uyku süresinde oksijen saturasyonun %90'nın altında kaldığı süre (ST_{90}), ST_{90}'nın toplam uyku süresine oranı (CT_{90}) ve en düşük oksijen saturasyonu (min

SaO_2) polisomnografiden (PSG) elde edildi. Tüm olguların beyin manyetik rezonans görüntülemerinde WMH ve SCI varlığı değerlendirildi.
Bulgular: Hipoksi parametreleri ST_{90}, CT_{90} ve min SaO_2 WMH varlığı ile anlamlı ilişkiliydi ($P < .001$). Multipl regresyon analizinde CT_{90} bağımsız olarak SCI ile birlikteydi ($P = 0.038$). İlave olarak, katılımcılar $CT_{90} < \%10$ ve $CT_{90} \geq \%10$ olarak iki gruba ayrıldığında, $CT_{90} \geq \%10$ grubunda yaş ($P = .002$), cinsiyet ($P= .015$), vücut kitle indeksi, apne-hipopne indeksi, Epworth uykululuk ölçeği, WMH varlığı, hipertensiyon ve diabetes mellitus $CT_{90} < \%10$ grubuna oranla anlamlı olarak daha yüksekti ($P < .001$, tüm parametrelerde). $CT_{90} \geq \%10$ olması WMH riskini 2.34 kat (95% CI 1.44 to 3.85, $P= 0.006$) arttırmaktadır.
Sonuç: OSA'de nokturnal intermittent hipoksi şiddeti WMH ve SCI patogenezine katkı sağlıyor olabilir.

Anahtar Kelimeler: Uyku apnesi, horlama, oksijen saturasyonu, hipoksi, inme, manyetik rezonans görüntüleme

INTRODUCTION

Obstructive sleep apnea (OSA) is a common syndrome characterized by repetitive episodic collapse of the upper airway and intermittent hypoxia during sleep. Disturbances in gas exchange lead to oxygen desaturation, hypercapnia, and fragmented sleep, which contribute to the metabolic, neurocognitive, and cardiovascular effects of OSA[16]. OSA is a common syndrome, affecting 3–7% of the general population[10,22]. Population-based studies suggest that up to 19% of middle-aged men and 15% of women may suffer from hypopnea and apnea[28]. OSA is an important risk factor for vascular diseases. However, the complex mechanisms underlying OSA and vascular diseases are not well understood[8].

The increased use of imaging techniques has allowed white matter hyperintensity (WMH) and silent cerebral infarcts (SCI) to be more commonly observed in asymptomatic patients[25]. The clinical importance of WMH constitutes a very important public health problem, as its association with incident stroke, dementia, and mortality has been highlighted in previous studies[7] Therefore, early detection of an SCI is important because it is associated with higher rates of mortality and subsequent clinical cerebral infarction[3,26]. Previous studies have shown that patients with moderate to severe OSA have a 2-fold increased risk of developing WMH and SCI[18,21]. Hypoxic processes and extreme changes in the vascular system that accompany apneic periods may injure the brain[15].

OSA severity can be determined by the Apnea-Hypopnea Index (AHI), which represents the frequency of apnea and hypopnea episodes per hour of sleep regardless of duration or morphology[2]. However, the AHI does not completely reflect the pathophysiological characteristics or severity of hypoxia[19]. Moreover, patients with similar AHI scores may have different clinical symptoms and outcomes[1,4]. Chronic intermittent hypoxia is usually defined as repeated episodes of hypoxia interspersed with periodic reoxygenation[20]. Total sleep duration with oxygen saturation < 90% (ST_{90}), percentage of cumulative time with oxygen saturation < 90% (CT_{90}), and the lowest oxygen saturation (min SaO_2) are directly associated with the duration and severity of hypoxia[4,19]. This study was conducted to determine the relationship between hypoxia parameters, such as ST_{90}, CT_{90}, and min SaO_2, and WMH and SCI on brain magnetic resonance (MR) images in patients with OSA.

MATERIAL AND METHODS

Study design and patients

The study group in this retrospective study was composed of 856 consecutive patients

suspected of having OSA who underwent a complete polysomnography (PSG) evaluation in our accredited sleep disorder center from April 2008 to October 2015. In total, 453 patients who underwent both PSG and brain MR imaging (MRI) were included in this study. The patient inclusion criterion for the study was no medical history of cerebrovascular diseases, such as ischemic stroke, transient ischemic attack, or intracerebral hemorrhage. Demographic and PSG data and information regarding age, sex, body mass index (BMI), and PSG parameters, such as total sleep duration, sleep efficiency, arousal index, AHI score, longest duration apnea episode, total apnea duration, ST_{90}, CT_{90}, and min SaO_2, were all recorded after obtaining approval from the institutional review board. Data on the duration of hypertension, smoking status, diabetes mellitus, coronary heart disease, and hyperlipidemia were mainly documented from the patients' medical records.

Patients with the following were excluded from the study: those who had central sleep apnea syndrome; narcolepsy; underwent previous treatment for OSA using continuous positive airway pressure, surgery, and/or an oral device; cerebrovascular disease; chronic obstructive pulmonary disease; bronchial asthma; dementia; renal failure; hepatic damage; malignancy; head trauma; brain tumor or malignancy; or were <18 years of age.

Informed consent could not be obtained due to the retrospective nature of this study. The study was evaluated by the Baskent University Institutional Review Board.

Polysomnography

All participants underwent PSG in a sleep laboratory using a computerized PSG device (E series, 44 channels; Compumedics, Victoria, Australia). Sixteen channels were used to document the following parameters: four-channel electroencephalogram, electro-oculogram, submental and leg electromyogram, electrocardiogram, nasal airflow using a nasal pressure cannula, air flow at the nose and mouth (thermistors), chest and abdominal respiratory movements, oxygen saturation (pulse oximetry), snoring via a microphone, and body position. Data from all participants were evaluated by a sleep specialist who was blinded to all information about the participants. Apnea was defined as cessation of air flow for at least 10 s with continued effort (obstructive) or lack of effort (central) to breathe. Hypopnea was defined as a >50% decrease in a valid air flow measure without the requirement for associated oxygen desaturation or arousal and with less reduction of air flow in association with oxygen desaturation >3% or arousal for at least 10 s. The AHI score was the number of apnea and hypopnea episodes per hour. ST_{90} was recorded in minutes. The min SaO_2 and CT_{90} were recorded as percentages. Sleep stages were evaluated according to the American Academy of Sleep Medicine criteria[2]. An AHI score < 5 was considered normal or simple snoring, 5 to <15 was considered mild OSA, 15 to <30 was considered moderate OSA, and ≥30 was considered severe OSA.

Magnetic resonance imaging

The presence of SCI and WMH was assessed by whole-brain MRI. The orbitomeatal line was considered the reference for all MRI brain scans (1.0 Tesla, Siemens Magnetom Vision Plus; Siemens, Munich, Germany). The scans included sagittal T1-weighted, axial T2-weighted, and axial fluid attenuated inversion recovery images. The slice thickness was 5 mm, the gap was 1 mm, and no intravenous contrast was used. All MRI scans were reviewed and scored by a radiologist who was blinded to the clinical details. The scans were visually assessed to determine the presence of WMH and SCI.

Statistical analysis

The data analysis was performed with IBM SPSS Statistics for Windows v. 21.0 statistical software (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (range). Categorical variables are presented as numbers or percentages. The normality of the continuous variable distributions was evaluated by the Kolmogorov–Smirnov test. Similarities between groups were assessed using Levene's variance test. Differences in continuous variables between the two groups were evaluated by independent sample t-tests or the Mann–Whitney test. Comparisons between more than two groups were evaluated by a one-way analysis of variance (ANOVA). Pairwise comparisons were evaluated with Tukey's test. Categorical variables were compared using Pearson's chi-square test. Factors affecting ST_{90}, CT_{90}, and min SaO_2 were determined by multiple logistic regression. A P-value ≤ 0.05 was considered significant.

RESULTS

Table **1** shows the patient characteristics. The median age of the patients was 51 years (range, 22–84 years), and most were males (69.2%). Table 2 shows the statistical differences in the parameters between the AHI groups. Male predominance was observed in all OSA groups (Table 2). The hypoxia parameters, such as ST_{90} and CT_{90}, were significantly higher but min SaO_2 was significantly lower in the OSA group compared with those in the control group (Table 2). WMH was more frequent in the OSA group than that in the control group (Table 2). Furthermore, SCI was observed more frequently in the severe OSA group compared with that in the control group (Table 2). Additionally, the odds ratio (OR) of WMH was 2.53-fold higher (95% confidence interval [CI], 1.60–3.98; P = 0.0001) in the OSA group (AHI ≥ 5) compared with that in the control group (AHI < 5). The OR of SCI was 3.41-fold higher (95% CI, 1.19–9.76; P = 0.02) in the OSA group (AHI ≥ 5; 345 patients) than that in the control group (AHI < 5; 108 patients).

The univariate analysis revealed a significant correlation between ST_{90} and age, BMI, AHI, Epworth Sleepiness Scale (ESS) score, CT_{90}, min SaO_2, hypertension, diabetes mellitus, and WMH (Table 3). Significant correlations were also revealed between CT_{90} and age, AHI score, BMI, ESS score, ST_{90}, min SaO_2, hypertension, coronary heart disease, hyperlipidemia, diabetes mellitus, and WMH (Table 3). Significant inverse correlations were observed between min SaO_2 and age, BMI, AHI score, ESS score, ST_{90}, CT_{90}, hypertension, coronary heart disease, hyperlipidemia, diabetes mellitus, and WMH (Table 3). Strong correlations were detected between the AHI score and ST_{90} and CT_{90} and min SaO_2, but the CT_{90} values varied, particularly among patients with severe OSA (Figure 1).

The multiple linear regression analysis revealed that AHI score (P < 0.001), age (P < 0.001), CT_{90} (P < 0.001), and min SaO_2 (P = 0.016) remained independent parameters affecting ST_{90} after adjusting for other confounders (Table 4). The multiple linear regression analysis also showed that AHI score (P < 0.001), age (P < 0.001), ST_{90} (P < 0.001), and SCI (P = 0.038) were independent parameters influencing CT_{90} after adjusting for other confounders (Table 4). AHI score (P < 0.001), age (P < 0.001), ST_{90} (P < 0.001), and BMI (P = 0.002) remained independent parameters influencing min SaO_2 after adjusting for other confounders (Table 4).

Additionally, the participants were divided into two groups according to CT_{90} < 10% (367 patients) and CT_{90} ≥ 10% (86 patients). Four (3.9%) of 103 patients in the mild OSA group had CT_{90} ≥ 10%; 4 (4.7%) of 86 patients in the moderate OSA group had CT_{90} ≥ 10%; and 78 (50%) of

156 patients in the severe OSA group had $CT_{90} \geq 10\%$ (Table 5 and Fig. 2). Seventy-eight of 86 patients (90.7%) who had $CT_{90} \geq 10\%$ were in the severe OSA group, and half of patients (78 of 156 patients) in the severe OSA group had $CT_{90} \geq 10\%$ (Table 5). The incidence rates of WMH, hypertension, and diabetes mellitus were significantly higher in the $CT_{90} \geq 10\%$ group than those in the $CT_{90} < 10\%$ group. SCI tended to be detected more frequently in the $CT_{90} \geq 10\%$ group than that in the $CT_{90} < 10\%$ group. These findings may be due to the limited number of patients rather than a lack of an effect of $CT_{90} \geq 10\%$ on SCI (Table 5). Age, AHI score, and ST_{90} values were significantly higher but the min SaO_2 value was significantly lower in the $CT_{90} \geq 10\%$ group than those in the $CT_{90} < 10\%$ group (Table 5). In addition, the OR of WMH was 2.35-fold higher (95% CI, 1.44–3.85; P = 0.0006) in the $CT_{90} \geq 10\%$ group than that in the $CT_{90} < 10\%$ group.

Table 1. Characteristics of study patients with obstructive sleep apnea*

Characteristic		**Number of Patients**	**(%)**
Sex	Female	139	30.7
	Male	314	69.4
AHI	AHI < 5	108	23.8
	AHI 5–15	103	22.7
	AHI 15–30	86	19.0
	AHI > 30	156	34.4
WMH	Absent	229	50.6
	Present	224	49.4
Silent cerebral infarct	Absent	409	90.3
	Present	44	9.7
Hypertension	Present	208	45.9
Coronary heart disease	Present	103	22.7
Hyperlipidemia	Present	87	19.2
Diabetes mellitus	Present	109	24.1
Hyperlipidemia	Present	87	19.2
Smoking	Present	91	20.1
Multinodular goiter	Present	32	7.1
		Mean ± SD	**Median [range]**
Age (y)		51.1 ± 13.3	51 [22–84]
Apnea-Hypopnea Index (events/h)		25.73 ± 24.97	16.7 [0–109]

Body mass index (kg/m^2)	31.32 ± 5.42	30.7 [18.2–50.1]
ST_{90} (min)	31.39 ± 64.21	3.8 [0–404.13]
CT_{90} (%)	7.42 ± 15.33	0.89 [0–96.1]
Total sleep time (min)	433.23 ± 48.77	437.08 [171–700]
Min SaO_2 (%)	82.19 ± 9.9	85 [35–98]
ESS	9.21 ± 5.64	9 [0–24]

*Data are mean ± standard deviation (SD), number of subjects (%), or median (range); CT_{90}, percentage of cumulative sleep time with oxygen saturation < 90%; min O_2, minimum O_2; ST_{90}, total sleep time with oxygen saturation < 90%; WMH, white matter hyperintensity; ESS, Epworth Sleepiness Scale

Table 2. Comparison of the Apnea-Hypopnea Index in patients with obstructive sleep apnea*

Characteristic	**Control**	**Mild OSA**	**Moderate OSA**	**Severe OSA**	***P* ≤** †
Apnea-Hypopnea Index (events/h)	<5	5 to <15	15 to <30	≥30	
No. of patients	108	103	86	156	
Age (y)	44.47 ± 12.69	52.58 ± 11.8	54.76 ± 12.19	54.27 ± 13.43	0.001‡
Sex — Female	52 (48.1)	41 (39.8)	22 (25.6)	24 (15.4)	0.001
Sex — Male	56 (51.9)	62 (60.2)	64 (74.4)	132 (84.6)	
Body mass index (kg/m^2)	27.83 ± 4.73	30.83 ± 5.12	32.25 ± 4.97	33.54 ± 5.02	0.001‡
Epworth Sleepiness Scale	8.14 ± 5.5	8.55 ± 5.16	8.85 ± 5.82	10.58 ± 5.73	0.002‖
ST_{90} (min)	0.17 (0–7.52)	1.2 (0–404.1)	5.7 (0–142)	40.86 (0.1–330)	0.001
CT_{90} (%)	0.04 (0–9.48)	0.28 (0–96.1)	1.3 (0–32.6)	9.17 (0.02–88.7)	0.001
Min SaO_2 (%)	90.23 ± 4.34	86.07 ± 4.86	81.3 ± 7.5	74.54 ± 10.58	0.001
Total sleep time (min)	433.9 ± 37.26	435.96 ± 49.22	439.22 ± 55.58	426.97 ± 51.22	NS
WMH	24 (31.6)	42 (57.5)	34 (48.6)	71 (62.3)	0.001¶
Silent cerebral infarct	4 (3.7)	12 (11.7)	7 (8.1)	21 (13.5)	0.008§

Hypertension	28 (25.9)	45 (43.7)	53 (61.6)	82 (52.6)	0.001
Coronary heart disease	9 (8.3)	27 (26.2)	27 (31.4)	40 (25.6)	0.002
Hyperlipidemia	12 (11.1)	21 (20.4)	18 (20.9)	36 (23.1)	NS
Diabetes mellitus	10 (9.3)	20 (19.4)	20 (23.3)	59(37.8)	0.001
Smoking	25 (23.1)	22 (21.4)	17 (19.8)	27 (17.3)	NS
Multinodular goiter	10 (9.3)	8 (7.8)	4 (4.7)	10 (6.4)	NS

*Data are mean ± SD, number of subjects (%), or median (range). CT_{90}, percentage of cumulative sleep time with oxygen saturation < 90%; min O_2, minimum O_2; OSA, obstructive sleep apnea; ST_{90}, total sleep time with oxygen saturation < 90%; WMH, white matter hyperintensity.
†NS, not significant ($P > 0.05$).
‡ The AHI < 5 group is different from the mild, moderate, and severe OSA groups.
§ The AHI < 5 group is different from the severe OSA group.
‖ The AHI ≥ 30 group is different from the AHI < 5, mild, and moderate OSA groups.
¶ The AHI < 5 group is different from the mild and severe OSA groups.

Table 3. Univariate analysis of factors affecting total sleep duration with oxygen saturation < 90% and the lowest oxygen saturation in patients with obstructive sleep apnea*

Variable	**ST_{90}**		**CT_{90}**		**Min SaO_2**	
	Correlation Coefficient	***P* ≤ †**	**Correlation Coefficient**	***P* ≤ †**	**Correlation Coefficient**	***P* ≤ †**
Age (y)	0.303	0.001	0.311	0.001	−0.329	0.001
Sex	0.188	NS	0.187	NS	−0.177	NS
Body mass index (kg/m^2)	0.393	0.001	0.395	0.001	−0.411	0.001
Apnea-Hypopnea Index (events/h)	0.772	0.001	0.768	0.001	−0.747	0.001
Epworth Sleepiness Scale	0.224	0.001	0.218	0.001	−0.239	0.001
ST_{90} (min)	-	-	0.994	0.001	−0.860	0.001
CT_{90} (%)	0.994	0.001	-	-	−0.856	0.001
Min SaO_2 (%)	−0.860	0.001	−0.856	0.001	-	-

Total sleep time (min)		−0.011	NS	−0.045	NS	0.059	NS
Hypertension	Absent	1.6 (0–314)	0.001	0.38 (0–85)	0.001	84 ± 10	0.001
	Absent	9.6 (0–404)		2.16 (0–96)		80 ± 10	
Coronary heart disease	Present	2.3 (0–330)	NS	0.53 (0–85)	0.002	83 ± 10	0.012
	Present	8.08 (0–404)		1.79 (0–96)		80 ± 10	
Hyperlipidemia	Absent	2.49 (0–404)	NS	0.59 (0–96)	0.017	82.9 ± 9.7	0.002
	Present	6.92 (0–297)		1.58 (0–70)		79.2 ± 10.2	
Diabetes mellitus	Absent	1.93 (0–330)	.001	0.43 (0–85)	0.001	83.67 ± 9.2	0.001
	Present	17.33 (0–404)		4.2 (0–96)		77.5 ± 10.7	
Smoking	Absent	3.9 (0–404)	NS	0.94 (0–96)	NS	82 ± 10	NS
	Present	2.67 (0–328)		0.59 (0–70)		84 ± 7	
Multinodular goiter	Absent	3.95 (0–404)	NS	0.93 (0–96)	NS	82 ± 10	NS
	Present	0.75 (0–212)		0.16 (0–56)		81 ± 10.69	
Silent cerebral infarct	Absent	3.3 (0–404)	NS	0.73 (0–96)	NS	82 ± 10	NS
	Present	7.05 (0–297)		1.57 (0–71)		81 ± 8	
WMH	Absent	1.88 (0–330)	0.012	0.42 (0–75)	0.001	84 ± 9	0.001
	Present	7.6 (0–404)		1.78 (0–96)		80 ± 10	

*Data are the correlation coefficient, mean ± SD, or median (range). CT_{90}, percentage of cumulative sleep time with oxygen saturation < 90%; min O_2, minimum O_2; ST_{90}, total sleep time with oxygen saturation < 90%; WMH, white matter hyperintensity; †NS, not significant ($P > 0.05$).

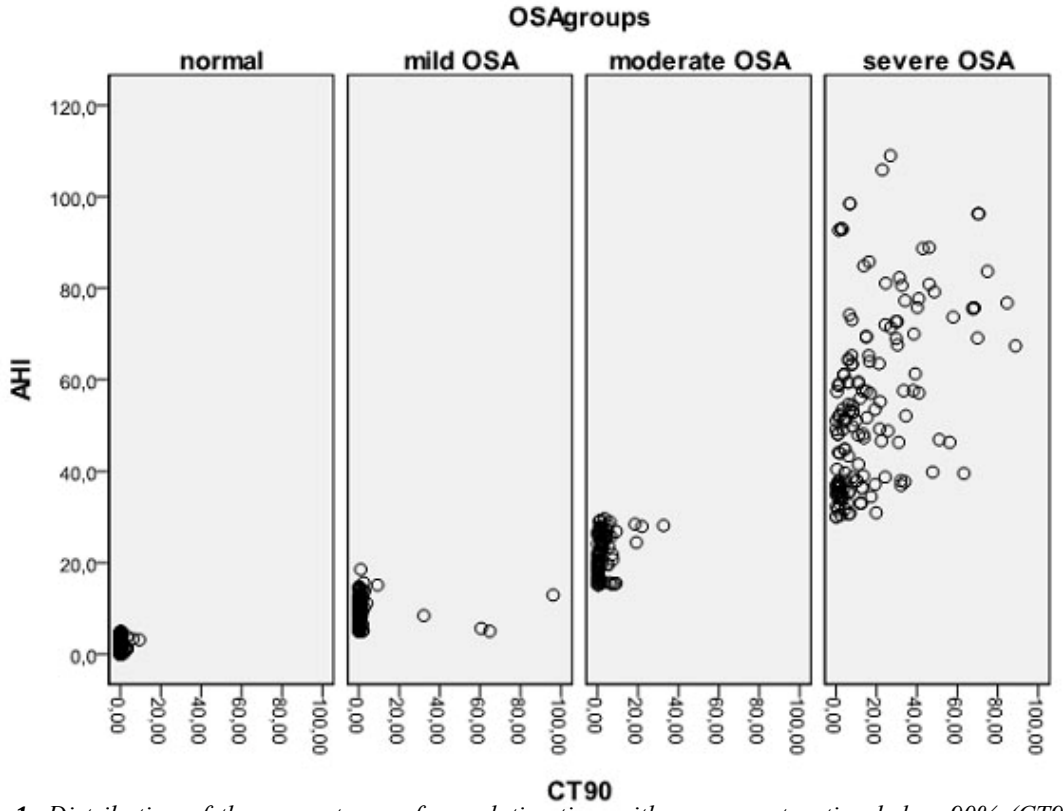

Figure 1: *Distribution of the percentages of cumulative time with oxygen saturation below 90% (CT90) values within different Apnea-Hypopnea Index (AHI) severity groups. OSA, obstructive sleep apnea. CT90 (%), AHI (events/h).*

Table 4. Multiple linear regression analysis of factors affecting total sleep duration with oxygen saturation < 90% and the lowest oxygen saturation in patients with obstructive sleep apnea*

Variable		**Coefficient**	**95% CI**	***P*** ≤ †
ST_{90}	Apnea-Hypopnea Index	0.670	0.399–0.940	0.001
	Age	1.249	0.180–2.319	0.001
	Min SaO_2	−2.926	−3.625 to −2.227	0.016
	CT_{90}	31.053	6.046–56.060	0.001
CT_{90}	Apnea-Hypopnea Index	−0.021	−0.025 to −0.001	0.001
	Age	0.024	0.009–0.047	0.003

	ST_{90}	0.993	0.232–0.242	0.001
	Silent cerebral infarct	0.017	0.050–1.716	0.038
Min SaO_2	Apnea-Hypopnea Index	−0.123	−0.159 to −0.087	0.001
	Age	−0.137	−0.191–0.082	0.001
	ST_{90}	−0.054	−0.068–0.041	0.001
	Body mass index (kg/m^2)	−0.432	−0.799 to −0.064	0.002

*Data are the correlation coefficients and 95% confidence intervals (CI); min SaO_2, minimum O_2; ST_{90}, total sleep time with oxygen saturation < 90%. †NS, not significant ($P > 0.05$).

Table 5. Distribution of the parameters according to percentage of cumulative time with oxygen saturation < 90% below and above 10%*

Parameters		**CT_{90} < 10 (n = 367)**		**CT_{90} ≥ 10%(n = 86)**		***P* ≤** †
Age (y)		50.54 ± 12.9		56.36 ± 13.88		0.002
Body mass index (kg/m^2)		30.49 ± 5.02		34.85 ± 6.64		0.001
ESS		8.62 ± 5.3		11.72 ± 6.22		0.001
Min SaO_2 (%)		85.42 ± 6.4		68.40 ± 10.33		0.001
Apnea-Hypopnea Index (events/h)		11.4 (0–98.5)		57.3 (5–109)		0.001
ST_{90} (minute)		1.67 (0–45.5)		109 (24.93–404.13)		0.001
CT_{90} (%)		0.39 (0–9.95)		26.88 (6.91–96.1)		0.001
		Number of patients	**(%)**	**Number of patients**	**(%)**	
Sex	Female	122	33.3	17	19.8	0.015
	Male	245	66.8	69	80.2	
Apnea-Hypopnea Index (events/h)	<5	108	29.4	-	-	0.001
	5 to <15	99	27	4	4.65	
	15 to <30	82	22.3	4	4.65	

≥30	78	21.3	78	90.7	
WMH	167	45.5	57	66.3	0.001
Silent cerebral infarct	32	8.7	12	14	NS
Hypertension	155	42.2	53	61.6	0.001
Coronary heart disease	82	22.3	21	24.4	NS
Hyperlipidemia	65	17.7	22	25.6	NS
Diabetes mellitus	69	18.8	40	46.5	0.001
Smoking	76	20.7	15	17.4	NS
Multinodular goiter	26	7.1	6	7	NS

*Data are the mean ± SD, number of subjects (%), or median (range). CT_{90}, percentage of cumulative sleep time with oxygen saturation < 90%; WMH, white matter hyperintensity; ESS, Epworth Sleepiness Scale. †NS, not significant ($P > 0.05$).

DISCUSSION

Our findings suggest a relationship between intermittent hypoxia and the presence of WMH and SCI in patients with OSA. The increased risk of WMH was 2.5-fold higher and the increase in the SCI risk was 3.4-fold higher in patients with OSA compared with those in the control group. Hypoxia parameters, such as ST_{90}, CT_{90}, and min SaO_2, were associated with WMH (Table 3). The multiple regression analysis showed that CT_{90} was independently associated with SCI (P = 0.038) (Table 4). Furthermore, $CT_{90} \geq 10\%$ led to a 2.35-fold increase in WMH risk compared with that of having $CT_{90} < 10\%$ (OR, 2.35; 95% CI, 1.44–3.84; P = 0.0006). These data suggest that increased severity of hypoxia may contribute to the pathogenesis of WMH and SCI in patients with OSA. This is the first report demonstrating a relationship between hypoxia severity and WMH and SCI in patients with OSA.

Previous studies have also reported that WMH and SCI occur more frequently in patients with OSA[5,18,21]. Eguchi et al. demonstrated that nocturnal hypoxia assessed by overnight pulse oximetry was independently associated with the prevalence of SCI among a high-risk community-dwelling Japanese population[11]. The mean age of participants in their hypoxia group (70 years old) was older than that of our patients (51 years old), and the male ratio was lower (31%) compared with that in our study (69%). The high female ratio and older age may have affected the findings[11]. Conflicting results have been reported in previous studies. Most previous studies failed to demonstrate a relationship between OSA and WMH and SCI[6,8,17]. The sample group was quite small in one study, and the mean age of participants in another study was older than that in the current study. Additionally, hypoxia was not considered in these studies. Robbins et al. reported that only central sleep apnea but not OSA was associated with the development of WMH[23]. These participants (mean age, 77 years), already had higher basal levels of WMH on their primary examinations. The negative findings may be explained by a survival bias or high rates of vascular risk factors, which are also commonly present in older adults. The participants in the current study

were younger (mean age, 51 years) compared with patients in other studies.

Furthermore, Zhang et al. reported a study of 119 patients with OSA who underwent velopharyngeal surgery. CT_{90} < 10% (grade 1 category) was an independent predictor of high surgical success[27]; however, the surgical success rate decreased dramatically when the hypoxia threshold was exceeded. In our study, only 4 (3.8%) of 103 patients with mild OSA and 4 (4.6%) of 86 patients with moderate OSA were in the $CT_{90} \geq 10\%$ category (Table 5). Among the patients in the $CT_{90} \geq 10$ % group, 90.7% were in the severe OSA group. Half of the patients with severe OSA (78 of 156 patients) were in the $CT_{90} \geq 10\%$ group, and AHI score, ESS, BMI, age, WMH, hypertension, and diabetes mellitus increased significantly above this threshold ($CT_{90} \geq 10\%$) (Table 5). The presence of SCI tended to be higher in the $CT_{90} \geq 10\%$ group, but the difference was not significant. This lack of an association may be due to the limited number of events rather than the lack of an effect. In addition, the risk of WMH increased 2.35-fold in the $CT_{90} \geq 10\%$ group compared to that in the $CT_{90} < 10\%$ group (Table 5).

The AHI score only indicates the number of apnea and hypopnea episodes per hour[2]. However, the AHI score does not reflect the actual duration or severity of hypoxia or disease outcome. Patients with similar AHI scores can have different durations and depths of cessation of breathing and oxygen desaturation. These differences mostly affect the symptoms and consequences of the disorder. Prolonged duration apnea and hypopnea episodes can paradoxically lead to a decrease in the AHI score, although it is commonly assumed that more severe health consequences are evident compared with those in patients with shorter events. Severe hypoxia despite a similar AHI score may cause severe physiological stress, cardiovascular consequences, or death[4,19].

Chronic intermittent hypoxia is a prominent characteristic of the pathophysiology of OSA. Repetitive episodes of hypoxia and reoxygenation occur more than 60 times per hour (hundreds of times per night) in cases of severe OSA and can last for years when hemoglobin desaturation reaches 50%[13]. This high frequency of hypoxia and reoxygenation cycles is similar to that observed in a patient with ischemia-reperfusion injury, resulting in increased production of reactive oxygen species and oxidative stress, which may contribute to OSA-associated cardiovascular pathologies[14]. Stopping breathing can lead to CO_2 retention and hypoxia, which disturbs the autonomic and hemodynamic responses during sleep[25]. Repetitively occurring apnea episodes are often followed by increased sympathetic activity, which can further lead to vasoconstriction of peripheral blood vessels[10].

The pathophysiology of WMH is heterogeneous. The presence of focal myleninolysis, axonal loss, and gliosis associated with vessel wall hyalinosis suggests that chronic hypoperfusion contributes to the development of WMH[12,24]. WMH are considered a subclinical stroke, and the same pathogenic mechanism occurs in patients with WMHs and stroke[24,26]. The ischemic effect of nocturnal apnea can increase with increased oxidative stress due to intermittent episodes of hypoxemia and reoxygenation. Thus, cerebrovascular endothelial dysfunction increases and autoregulation deteriorates, which preferentially damage small vessels in the brain[25].

Some limitations of our study should be mentioned. A retrospective study has inherent problems, such as biased patient selection and a single-institutional analysis, which can lead to prejudgment and referral bias. In addition, patients with various vascular factors, such as coronary heart disease, hypertension, hyperlipidemia,

diabetes mellitus, smoking, and obesity, were not strictly excluded from the study. Comparing the results with different levels of other thrombotic and endothelial dysfunction markers may improve the understanding of OSA pathophysiology. Furthermore, the MRI was not performed immediately after PSG, and we did not evaluate the localization or number of WMH.

In conclusion, the severity of nocturnal intermittent hypoxia may contribute to the pathogenesis of WMH and SCI in patients with OSA. Hypoxia parameters, such as ST_{90}, CT_{90}, and min SaO_2, should be screened to detect hypoxemia occurring due to OSA.

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