



# Correlation between Carotid Arterial Calcium Score and Silent Cerebrovascular Lesions in Obstructive Sleep Apnea Patients: by Using Upper Airway CT and Brain MRI

수면무호흡증 환자에서 경동맥 석회화 점수와 무증상 뇌혈관병변에 대한 상관관계: 상기도 전산화단층촬영 검사와 뇌 자기공명영상을 이용한 연구

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**Purpose** To investigate the relationship between carotid arterial calcium score (CarACS) and silent cerebrovascular lesions in patients with obstructive sleep apnea (OSA).

**Materials and Methods** This study involved retrospective evaluation of 60 OSA patients who underwent both upper airway CT and brain MRI. Using polysomnography, several indicators, including apnea index (AI), were used to evaluate the relationship between OSA and silent cerebrovascular lesions. The CarACS was quantified on CT imaging using the modified Agatston method. Silent cerebrovascular lesions were evaluated on brain MRI by grading periventricular hyperintensity (PVH). Various clinical characteristics, including age, were analyzed in each patient.

**Results** The number of patients per PVH grade 0, 1, 2, 3, and 4 was 26 (43.3%), 14 (23.3%), 14 (23.3%), 4 (6.7%), and 2 (3.3%), respectively. The mean age, hypertension, smoking status, AI, and CarACS were significantly different among PVH groups ( $P < 0.05$ ). In univariate analysis, the presence of carotid arterial calcification ( $\beta = 0.483$ ,  $p < 0.01$ ), CarACS ( $\beta = 0.482$ ,  $p < 0.01$ ), and age ( $\beta = 0.360$ ,  $p < 0.01$ ) showed a significant association with PVH grade. The mean AI and lowest O<sub>2</sub> saturation had statistically weak associations with PVH grade ( $\beta = 0.267$ ,  $p < 0.01$ ;  $\beta = -0.219$ ,  $p < 0.14$ , respectively). In multivariate analysis, CarACS was the only factor affecting PVH

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grade ( $p < 0.04$ ).

**Conclusion** CarACS is associated with the severity of silent cerebrovascular lesions. Therefore, additional analysis of CarACS in OSA patients may provide more information on their cerebrovascular status.

**Index terms** Obstructive Sleep Apnea; Carotid Arteries; Calcium; Cerebrovascular Disorders; Cerebral Ischemia; Magnetic Resonance Imaging

## INTRODUCTION

Obstructive sleep apnea (OSA) is sleep-disordered breathing that is characterized by periods of obstructed breathing during the night, which lead to intermittent and repetitive hypoxia and recurrent arousals during sleep. The prevalence of OSA varies from country to country and ranges from 9% to 38% among general population (1). Many studies have shown that OSA is associated with a relatively higher prevalence of coronary heart disease, heart failure, and stroke (2-4). Moreover, Munoz et al. (5) reported that patients with severe OSA have an increased risk of developing a stroke (hazard ratio = 2.52).

Silent cerebrovascular lesions, seen as white matter hyperintensity and lacunar infarcts, are a common incidental finding on brain MRI and are considered to be part of the preconditioning phase of cerebrovascular events such as stroke from a preventive medical point of view (6-10). Vermeer et al. (6) reported that the presence of silent cerebrovascular lesions increases the risk of stroke more than three-fold (adjusted hazard ratio 3.0, 95% confidence interval 2.3 to 6.8). Thus, the assessment of silent cerebrovascular lesions may have the ability to predict cerebrovascular disease (CVD). The silent cerebrovascular lesions can be evaluated in various ways on brain MRI and one method is using periventricular hyperintensity (PVH) and patients with severe OSA show a higher prevalence of silent cerebrovascular lesions than those with mild OSA (8-10).

Physicians (dentists or otolaryngologists) in a sleep clinic obtain a cephalometric radiograph or airway CT scan to assess a patient's craniofacial and airway anatomy and to manage the plan for comorbid disease in patients with OSA. Sometimes, carotid arterial calcification (CarAC) is observed in the images of a cephalometric radiograph and airway CT (11, 12). Several studies demonstrated the feasibility of quantifying CarAC with a three-dimensional (3D) carotid CT scan by using the Agatston's method (Agatston score), which has been widely used to quantify calcification of the coronary arteries and predict cardiovascular events (13-17). Bos et al. (18) suggested that CarAC is associated with the presence of cerebral infarcts in the elderly. Therefore, it may be meaningful to obtain additional information related to CVD using CarACS. However, according to our findings, there has been no study about the association between the CarACS (carotid arterial calcium score) calculated with CT and silent cerebrovascular lesions graded with MRI in patients with OSA. The purpose of our study is to investigate the relationship of CarACS measured on airway CT with a modified Agatston method and silent cerebrovascular lesions quantified on brain MRI with PVH grading system in patients with OSA.

## MATERIALS AND METHODS

### SUBJECTS

In total, 489 consecutive patients who had undergone polysomnography (PSG) for OSA problem from March 2011 to March 2018 were enrolled. All patients with OSA were routinely subject to upper airway CT to understand their airway morphology and accompanying diseases. Among the 489 subjects, 60 consecutive OSA patients (45 males; mean age,  $54.5 \pm 10.8$  years old; age range, 19–77 years old) who underwent the brain MRI for clinical necessity [neurologic symptoms (dizziness, headache, etc.,  $n = 42$ ); cognitive impairment ( $n = 10$ ); anxiety ( $n = 2$ )] or for a health checkup ( $n = 6$ ) were enrolled as subjects (Table 1). In the meantime, we excluded people with silent cerebrovascular lesions mimicking diseases such as adult-onset leukoencephalopathies or demyelinating disease that cause white matter hyperintensities on MRI by using other radiologic findings and medical history (7). However, no patient showed evidence of these problems and thus all 60 patients were included as subjects.

This is a retrospective study. The institutional ethics committee approved this study, and written informed consent was waived (IRB No. DAUHIRB-17-113).

### POLYSOMNOGRAPHY

Overnight PSG (Alice 5, 19 channels; Philips Respironics, Inc., Kennesaw, GA, USA) was used to diagnose OSA in all patients. In this study, apnea was identified by  $> 90\%$  reduction of airflow for at least 10 s and hypopnea was identified by  $\geq 30\%$  decrease in airflow for at least 10 s, combined with an arousal and/or 3% oxygen desaturation. The apnea index (AI) and hypopnea index (HI) are the average number of apnea and hypopnea events per hour of sleep, respectively. Respiratory effort related arousals (RERAs) were identified as increased respiratory efforts for at least 10 s, followed by an abrupt arousal from deeper sleep, but which did not meet the criteria for apnea or hypopnea. The apnea-hypopnea index (AHI) was defined as the average number of apnea events plus hypopneas events per hour of sleep. The respiratory disturbance index (RDI) is the average number of combined apnea events, hypopnea events, and RERA events per hour during sleep ( $RDI = \text{apnea} + \text{hypopnea} + \text{RERAs per hour of sleep}$ ). Lowest  $O_2$  saturation during sleep is one of indices, used to express the severity of oxygen desaturation during PSG.

### MEASUREMENT OF CAROTID ARTERIAL CALCIFICATION

#### CT PARAMETER

Within 1 week of the PSG examination, all patients routinely underwent non-contrast airway CT scans with a 320-detector-row scanner (Aquilion ONE; Canon Medical Systems Corporation, Otawara, Japan). The image range of the airway CT scan captured an area from the frontal sinus of the skull to the carina level of the distal trachea to embrace both nasal and intra-thoracic airways (Fig. 1). The airway CT scan was set up with the following parameters: collimation,  $320 \times 0.5$  mm; gantry rotation time, 500 ms; tube voltage, 120 kV; tube current, 80 mA; slice thickness, 0.5 mm. All datasets were processed with iterative reconstruction (3D

Table 1. General Characteristics of Enrolled Subjects

Characteristics	
No. of patients	60
Age (years)	54.5 ± 10.8
Male sex	45 (75)
BMI (kg/m <sup>2</sup> )	26.2 ± 3.4
Smoking	
Never	36 (60)
Past	7 (11.7)
Current	17 (28.3)
Hypertension*	26 (43.3)
Systolic BP (mm Hg)	130.2 ± 16.0
Diastolic BP (mm Hg)	78.8 ± 12.9
Diabetes mellitus <sup>†</sup>	8 (13.3)
Cerebrovascular event	11 (18.3)
Total cholesterol (mg/dL)	187.2 ± 47.2
HDL cholesterol (mg/dL)	54.4 ± 11.9
LDL cholesterol (mg/dL)	112.3 ± 31.5
ESS	9.5 ± 4.4
RDI (events/h)	31.8 ± 25.9
AI (events/h)	16.3 ± 22
HI (events/h)	14.9 ± 11.3
AHI (events/h)	29.7 ± 25.9
RERA (events/h)	2.5 ± 4.1
Lowest O <sub>2</sub> saturation	82.8 ± 8.9
CarAC	15 (25)
CarACS	45.7 ± 151.7
Log (CarACS + 1)	0.97 ± 1.96
CarACS groups	
0	46 (76.7)
1–10	1 (1.7)
11–100	7 (11.7)
101–400	3 (5)
> 400	3 (5)
PVH grade	
0	26 (43.3)
1	14 (23.3)
2	14 (23.3)
3	4 (6.7)
4	2 (3.3)

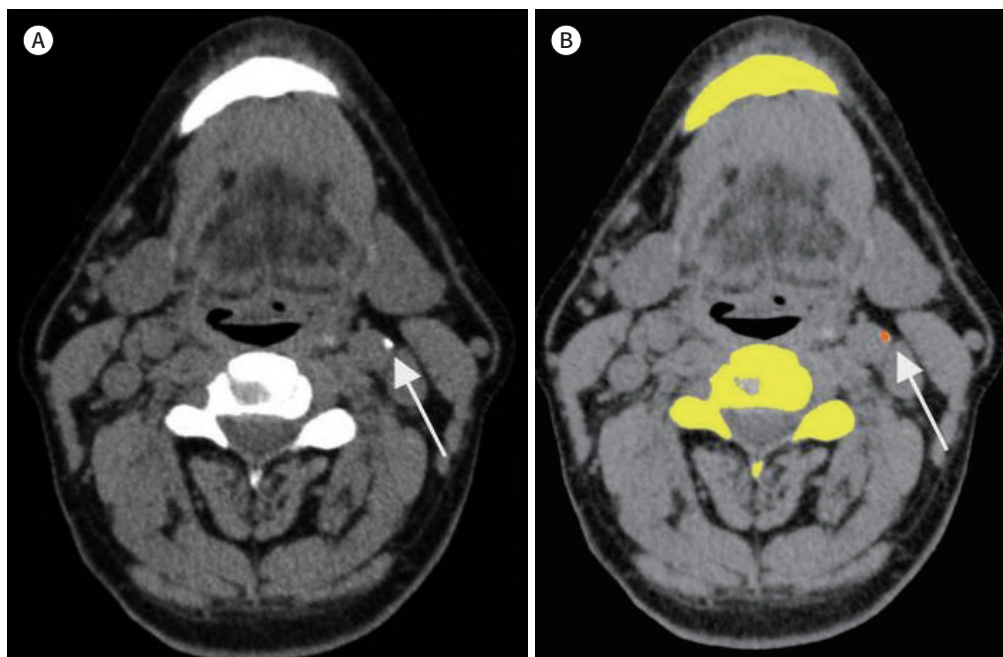
Data are expressed as mean ± standard deviation or numbers of patients (%).

\*Patients were considered hypertensive if their BP was consistently > 140/90 mm Hg, or if they were currently taking antihypertensive medication.

<sup>†</sup> Patients were considered to have diabetes mellitus if their fasting glucose level was ≥ 126 mg/dL, at least in one assessment, or if they were currently taking oral hypoglycemic agents or insulin.

AHI = apnea-hypopnea index, AI = apnea index, BMI = body mass index, BP = blood pressure, CarAC = carotid arterial calcification, CarACS = carotid arterial calcium score, ESS = Epworth sleepiness scale, HDL = high-density lipoprotein, HI = hypopnea index, LDL = low-density lipoprotein, PVH = periventricular hyperintensity, RDI = respiratory disturbance index, RERA = respiratory effort-related arousals

**Fig. 1.** Representative images of measurement of carotid arterial calcification with upper airway CT scan.  
**A.** The arrow indicates calcification in the left common carotid artery on upper airway CT scan.  
**B.** Reconstructed image of upper airway CT to measure carotid arterial calcificum score. Calcification is shown as the red-colored area (arrow) and is semi-automatically calculated by the modified Agatston method.



adaptive iterative dose reduction), with a 3-mm slice thickness and a 3-mm interval. The images were then transferred to commercial software (Vitreia 6.0; Vital Images, Minnetonka, MN, USA) for post-processing and analysis.

### ANALYSIS OF CarACS

The CarACS was quantified using the modified Agatston method which is a well-known and validated quantitative parameter adopted to assess calcium in coronary arteries. On axial CT images, the software automatically highlights densities greater than 130 Hounsfield units (HU) in a 1 mm<sup>2</sup> area (Fig. 1). The calcium score was calculated as the product of the lesion areas and a cofactor between 1 and 5 (cofactor 1, 0 HU; cofactor 2, 1–10 HU; cofactor 3, 11–100 HU; cofactor 4, 101–400 HU; cofactor 5, > 400 HU). An experienced radiologist performed the measurement of CarACS using semi-automated scoring, and particular attention was paid to exclude bony spurs or calcified ligamentous structures. Calcification in the common, external, and internal carotid arteries was measured to calculate CarACS. The total CarACS was estimated as the sum of these scores.

### MEASUREMENT OF SILENT CEREBROVASCULAR LESION

All brain MRIs were scanned within 3 years before or after the airway CT scan. The examinations were performed utilizing a 1.5 Tesla MRI system (Signa Excite; GE Medical Systems, Milwaukee, WI, USA) or a 3 Tesla MRI system (Discovery MR 750; GE Healthcare, Waukesha, WI, USA) for a screening or evaluation of cerebrovascular lesion between March 2011 and March 2018. T2-weighted fluid-attenuated inversion recovery (FLAIR) parameters for the two

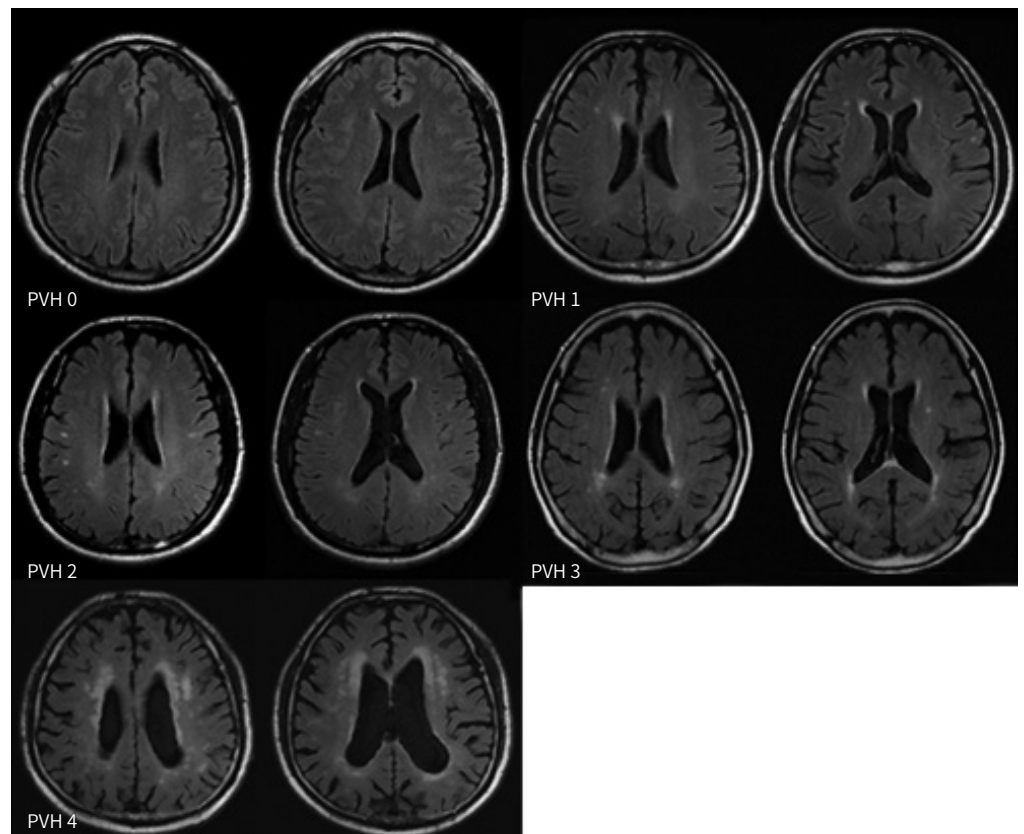
scanners were as follows: repetition time/echo time = 10000/141 ms, TI = 2569 ms, field of view =  $21 \times 21$  cm, matrix size =  $160 \times 160$ , slice thickness = 5 mm, interslice gap = 1.5 mm, b value =  $1000 \text{ s/mm}^2$ . The resulting voxel volumes of FLAIR were  $8.61 \text{ mm}^3$ .

Image analysis was performed using a PACS viewer (INFINITT PiviewSTAR, Infinit Health-care, Seoul, Korea). Two trained radiologists blinded to the patients' clinical information such as the degree of CarAC on upper airway CT performed the grading of silent cerebrovascular lesions on brain MRI. The presence of silent cerebrovascular lesions was evaluated on whole brain MRI with T2-weighted and FLAIR images by scoring PVH. The degree of PVH was classified according to Fukuda et al. (19, 20); PVH 0, no PVH detected; PVH 1, PVH detected in the apex of the frontal or posterior horn; PVH 2, mild PVH detected along the lateral ventricle; PVH 3, PVH strongly detected along the entire lateral ventricle; and PVH 4, diffuse PVH detected in the deep white matter (Fig. 2). If the interpretation of PVH grade differed between two radiologists, it was resolved through a consensus after discussion.

## CLINICAL ANALYSIS

The clinical histories of the subjects were reviewed retrospectively within 1 month of the CT study, which included the following: history of comorbid diseases (e.g., hypertension, diabetes mellitus, and smoking), lipid profile (total cholesterol, high-density lipoprotein, and low-

**Fig. 2.** Representative images of PVH. PVH grade was evaluated on T2-weighted fluid-attenuated inversion recovery sequence of the brain MRI.  
PVH = periventricular hyperintensity





density lipoprotein), blood pressure, body weight/height, and body mass index (BMI). Epworth sleepiness scales (ESS), from a simple self-administered questionnaire that is shown to provide a measurement of a subject's general level of daytime sleepiness (0–24 score), were obtained from all subjects just before PSG examination (21).

## STATISTICAL ANALYSIS

The results of PSG, the CarACS, and various clinical characteristics were compared among the 5 different PVH groups (PVH grade 0–4). The independent *t*-test was used for continuous variables, and Fisher's exact test was used for binomial variables. The Kruskal-Wallis test or Mann-Whitney U-test was performed for non-normally distributed variables, according to the results produced by the Kolmogorov-Smirnov test. The CarACS was also analyzed by logarithmic transformation after adding a constant of 1 to each score due to the wide range of values. The associated factors for high PVH grade were first examined using a univariate Cox proportional hazards model, and variables with a significant association ( $p < 0.20$ ) were applied to a multivariate Cox proportional hazards model. All data was analyzed by SPSS (version 20.0; IBM Corp., Armonk, NY, USA).  $p$ -value  $< 0.05$  were considered significant.

We used the intraclass correlation coefficient (ICC), which is an index of concordance about grading of the PVH between two readers. ICC values of 0.00–0.20 were indicative of poor agreement; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good agreement; and 0.81 or more, very good agreement.

## RESULTS

### GENERAL CHARACTERISTICS OF THE ENROLLED SUBJECTS

Of the 60 subjects, 75% were of male sex (45 patients), 17 patients were current smokers (28%), 26 patients had hypertension (43%), 8 patients had diabetes (13%), and 11 patients (18.3%) had a history of CVD events (Table 1). According the PSG results, the mean RDI was  $31.8 \pm 25.9$  events/h and the mean AI was  $16.3 \pm 22$  events/h. The mean lowest O<sub>2</sub> saturation was  $82.8 \pm 8.9\%$ . On the airway CT, CarAC was found in 14 patients (23%) and the mean CarACS was  $45.74 \pm 112.3$ . On the brain MRI, 26 patients (43.3%) showed a PVH grade of 0. There were 14 patients (23.3%) in each of PVH grades 1 and 2, 4 patients (6.7%) having a PVH grade of 3, and 2 patients (3.3%) in PVH grade 4, respectively (Tables 1 and 2). The scoring of PVH showed very good agreement between two radiologists (ICC = 0.961).

### COMPARISON OF MEAN VALUES FOR EACH OF THE PVH GRADE GROUPS

The mean patient age showed a significant difference among the 5 PVH groups ( $p = 0.018$ ), and high grade groups showed relatively older age (PVH grade 0,  $50.5 \pm 10.3$ ; PVH grade 1,  $55.5 \pm 6.8$ ; PVH grade 2,  $55.9 \pm 12.7$ ; PVH grade 3,  $63.5 \pm 9$ ; PVH grade 4,  $68.5 \pm 12$  years old). Smoking history differed significantly among the PVH groups, with more than half of patients being non-smokers for life in the PVH grade 0 group while all patients were current smokers in the PVH grade 4 group ( $p = 0.005$ ). Subjects with hypertension were distributed significant differently among groups, and the PVH grade 4 group showed the highest prevalence of hypertension (100% in PVH grade 4,  $p = 0.036$ ). The other general characteristics in-

cluding male sex, BMI, prevalence of diabetes, mean cholesterol and ESS score did not differ among the five groups. In the PSG results of the subjects, only AI showed significant differences among the PVH groups, and there were no differences in the other PSG results including mean RDI, HI, RERA, lowest O<sub>2</sub> saturation and OSA severity (AI,  $p = 0.044$ ). Meanwhile, all data related to CarAC such as the presence and absence of CarAC, CarACS, Log (CarACS + 1), and CarACS group demonstrated a significant difference among the PVH grade groups ( $p < 0.002$ ,  $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.001$ , respectively) (Table 2).

**Table 2.** Comparison of Mean Values for Each PVH Grade

	PVH Grade					p-Value
	0	1	2	3	4	
No. of patients	26	14	14	4	2	
Age	50.5 ± 10.3	55.5 ± 6.8	55.9 ± 12.7	63.5 ± 9	68.5 ± 12	0.018
Male sex	17 (65.4)	13 (92.9)	10 (71.4)	3 (75.0)	2 (100.0)	0.352
BMI (kg/m <sup>2</sup> )	25.5 ± 2.8	26.9 ± 3	26.3 ± 3.4	27.9 ± 8.6	27.7 ± 0.1	0.578
Smoking						0.005
Never	15 (57.7)	4 (28.6)	13 (92.9)	4 (100.0)	0 (0.0)	
Past	5 (19.2)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Current	6 (23.1)	8 (57.1)	1 (7.1)	0 (0.0)	2 (100.0)	
Hypertension	9 (34.6)	9 (64.3)	3 (21.4)	3 (75.0)	2 (100.0)	0.036
Diabetes mellitus	3 (11.5)	2 (14.3)	2 (14.3)	1 (25.0)	0 (0.0)	0.935
Total cholesterol (mg/dL)	181.1 ± 39.2	173.7 ± 32.9	184.6 ± 38.4	189.5 ± 74.8	105 ± 127.4	0.880
HDL cholesterol (mg/dL)	51.4 ± 10.1	50 ± 14.8	47.5 ± 11.7	57.8 ± 13.3	52 ± 0	0.846
LDL cholesterol (mg/dL)	113.2 ± 31.6	103.6 ± 28.6	115 ± 29.5	123.8 ± 45.3	76 ± 0	0.670
ESS	8.9 ± 3.9	11 ± 5.2	10.3 ± 4.3	8.8 ± 5.6	7.5 ± 0.7	0.650
RDI (events/h)	24 ± 19.9	42.7 ± 31.7	28.3 ± 19.9	60.4 ± 41.2	25.8 ± 18.2	0.157
AI (events/h)	8.4 ± 13.6	26.3 ± 26.7	12.4 ± 12.7	49.9 ± 38.3	16.3 ± 21.7	0.044
HI (events/h)	14.4 ± 11.7	15.7 ± 11.7	17.2 ± 12.4	8.5 ± 4.6	9.6 ± 3.5	0.331
AHI (events/h)	21.9 ± 19.2	39 ± 33	27.5 ± 19.5	58.4 ± 42.5	25.8 ± 18.2	0.244
RERA (events/h)	2.4 ± 3.6	4.7 ± 6.5	1 ± 2	4.1 ± 0.1	0 ± 0	0.078
Lowest O <sub>2</sub> saturation	84.5 ± 9.7	80.8 ± 6.3	83.9 ± 7	74.3 ± 14.1	80.6 ± 3.4	0.278
CarAC	1 (3.8)	6 (42.9)	3 (21.4)	2 (50.0)	2 (100.0)	0.002
CarACS	5.9 ± 29.9	65.9 ± 157.9	1.7 ± 4.3	90.9 ± 167.1	663.5 ± 322.1	0.001
Log (CarACS + 1)	0.19 ± 0.99	1.84 ± 2.37	0.40 ± 0.92	2.25 ± 2.82	6.44 ± 0.51	0.001
CarACS group						0.001
0	25 (96.2)	8 (57.1)	11 (78.6)	2 (50.0)	0 (0.0)	
1-10	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	
11-100	0 (0.0)	4 (28.6)	2 (14.3)	1 (25.0)	0 (0.0)	
101-400	1 (3.8)	1 (7.1)	0 (0.0)	1 (25.0)	0 (0.0)	
400	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	2 (100.0)	

Data are expressed as mean ± standard deviation or numbers of patients (%). Kruskal-Wallis test was performed for non-normally distributed variables.

AHI = apnea-hypopnea index, AI = apnea index, BMI = body mass index, CarAC = carotid arterial calcification, CarACS = carotid arterial calcium score, ESS = Epworth sleepiness scale, HDL = high-density lipoprotein, HI = hypopnea index, LDL = low-density lipoprotein, PVH = periventricular hyperintensity, RDI = respiratory disturbance index, RERA = respiratory effort-related arousals



## ASSOCIATED FACTORS WITH HIGH PVH GRADE BY COX ANALYSIS

A univariate linear regression model revealed that the Log (CarACS + 1) [standardized coefficient ( $\beta$ ) = 0.485,  $p < 0.001$ ] and age ( $\beta$  = 0.360,  $p = 0.010$ ) showed significant association with PVH grade. The mean AI and lowest O<sub>2</sub> saturation had a weak association with PVH grade, but neither were statistically significant. The male sex, BMI, smoking history, hypertension, diabetes, cholesterol levels, ESS, HI, RERA, and RDI were not statistically associated with PVH grade. In multivariate linear regression analysis, we adjusted for factors reached  $p < 0.20$  by univariate analysis. The Log (CarACS + 1) ( $\beta$  = 0.283,  $p = 0.038$ ) was the only significant factor for PVH grade and age ( $\beta$  = 0.245,  $p = 0.065$ ) did not show a statistically significant value (Table 3, Figs. 3, 4).

## DISCUSSION

In the comparison of each PVH groups, mean values of age, hypertension, smoking, AI and CarACS showed significant differences among the PVH groups. The associated factors with high PVH grade were AI, lowest O<sub>2</sub> saturation and CarACS. Among those, CarACS was statistically significant independent factor after adjusting for the influence of other factors.

**Table 3.** Factors Associated with High PVH Grade by Cox Analysis

Variables	Univariate			Multivariate*		
	$\beta$	SE	p-Value	$\beta$	SE	p-Value
Age	0.360	0.015	0.010	0.245	0.013	0.065
Male	0.050	0.375	0.728			
BMI	0.172	0.053	0.242			
Smoking	-0.073	0.181	0.616			
Hypertension	0.089	0.329	0.537			
Diabetes mellitus	-0.015	0.476	0.921			
Total cholesterol	-0.072	0.004	0.685			
HDL cholesterol	0.047	0.020	0.818			
LDL cholesterol	0.088	0.007	0.669			
ESS	0.026	0.038	0.865			
AI	0.267	0.009	0.070	0.176	0.008	0.243
HI	-0.143	0.017	0.336			
AHI	0.153	0.007	0.287			
RERA	-0.134	0.042	0.415			
RDI	0.120	0.007	0.405			
Lowest O <sub>2</sub> saturation	-0.219	0.018	0.139	-0.028	0.019	0.847
CarAC	0.483	0.337	< 0.001			
CarACS	0.482	0.001	< 0.001			
Log (CarACS + 1)	0.485	0.073	< 0.001	0.283	0.075	0.038

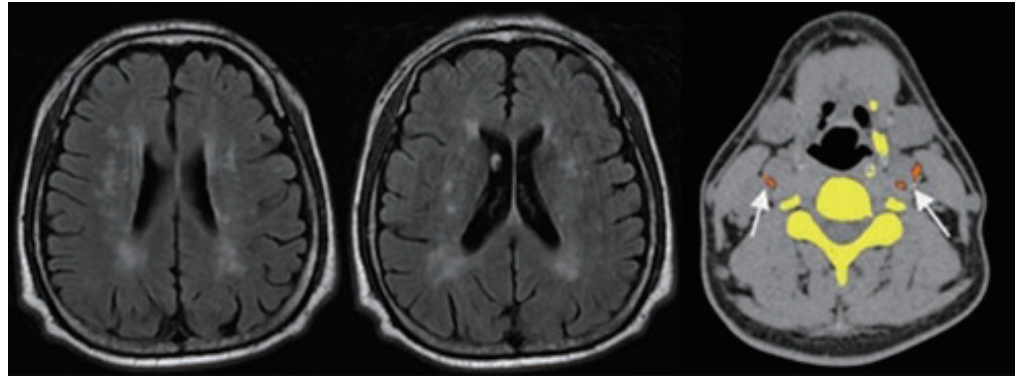
$R^2 = 0.274$ , Adj- $R^2 = 0.219$ , F-value = 4.914,  $p = 0.002$ .

\*The multivariate model includes variables with  $p < 0.20$  by univariate analysis.

$\beta$  = standardized coefficient, AHI = apnea-hypopnea index, AI = apnea index, BMI = body mass index, CarAC = carotid artery calcification, CarACS = carotid arterial calcium score, ESS = Epworth sleepiness scale, HDL = high-density lipoprotein, HI = hypopnea index, LDL = low-density lipoprotein, RDI = respiratory disturbance index, RERA = respiratory effort-related arousals, SE = standard error

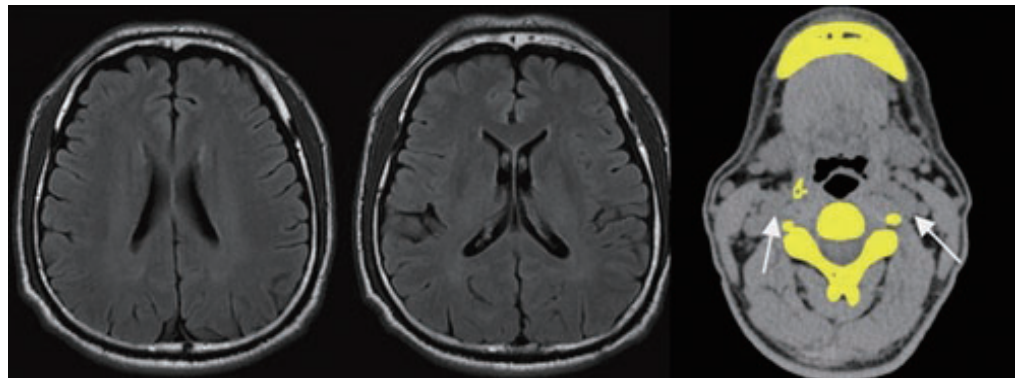
**Fig. 3.** Representative patient with a PVH grade 4 and high CarACS. A 60-year-old man with a PVH grade 4 as determined by brain MRI was included in the highest CarACS group with a score of 435 on upper airway CT (arrows indicate CarAC). The results of polysomnography were as follows: RDI 38.7 events/h, AI 31.6 events/h, lowest O<sub>2</sub> saturation 78.2%. He was a smoker and had hypertension.

AI = apnea index, CarAC = carotid artery calcification, CarACS = carotid arterial calcium score, PVH = periventricular hyperintensity, RDI = respiratory disturbance index



**Fig. 4.** Representative patient with a PVH grade 1 and no CarAC. A 59-year-old man showed PVH only in the apex of the frontal horn of the lateral ventricle on brain MRI (PVH grade 1). On upper airway CT, he showed no CarAC (CarACS = 0) (arrows indicate the common carotid artery). The results of polysomnography were as follows: RDI 35.1 events/h; AI 10.6 event/h; lowest O<sub>2</sub> saturation 83%. He was also a smoker.

AI = apnea index, CarAC = carotid artery calcification, CarACS = carotid arterial calcium score, PVH = periventricular hyperintensity, RDI = respiratory disturbance index



In our study, there were statistically significant differences in age, hypertension, and smoking among the five PVH groups. The elderly had a tendency for higher PVH grades, and patients in the PVH 4 group were all smokers and had hypertension. These factors are well known as risk factors for the development of CVD and our results are similar (7, 22, 23).

In univariate analysis, AI and lowest O<sub>2</sub> saturation showed a weak association with PVH grade although the value of RDI showed no significant association with PVH grade. OSA is known as a risk factor for CVD (1, 2, 5). However, it remains unclear whether OSA is an independent or accelerating factor (coexisting with other atherogenic risk factors) for developing silent cerebrovascular lesions, which are the precondition of cerebrovascular events. Davies et al. (24) reported that OSA may be related to an excess of cerebrovascular risk rather than to cerebrovascular damages themselves with qualitatively observed white matter grade evaluation in OSA patients. Kiernan et al. (25) also showed that there is no significant relationship

between OSA and white matter changes. However, Gunbatar et al. (26) reported that moderate to severe ( $\text{AHI} \geq 15/\text{h}$ ) OSA patients have a higher prevalence of silent cerebrovascular lesions than a control group ( $p = 0.028$ ). We found it is worth considering that the AI and lowest  $\text{O}_2$  saturation correlated with PVH grades.

Various mechanisms are related to apnea or lowest  $\text{O}_2$  saturation. It is reported that a decreased cerebral perfusion pressure associated with apnea causes abnormal cerebrovascular hemodynamics, which increase intracranial pressure and hypercapnia related apnea, while the subsequent changes in cerebral blood flow velocity and vessel wall tension causes long-term damage of cerebral blood vessels (27, 28). Patel et al. (29) suggested that nocturnal hypoxemia, which is related to low saturation, may be considered as an independent indicator of silent cerebrovascular lesions among various indicators related to OSA. Zuurbier et al. (30) also reported that oxygen desaturation mainly explains the association between OSA and brain damage. Our results about AI and lowest  $\text{O}_2$  saturation are relatively concordant with results of these researchers.

PVH grade was associated with CarACS as well as age, which is a conventional risk factor in patients with OSA (2). (Representative cases are shown in Figs. 3, 4). The association between CarACS and PVH grade persisted, even after adjusting for all traditional atherogenic risk parameters, whereas the effect of age disappeared. Although the pathophysiology of silent cerebrovascular lesions is not clearly known in the general population, ischemia, infarction, inflammation, increased vascular permeability, and venous insufficiency have all been suggested as causes of silent cerebrovascular lesions. After all, silent cerebrovascular lesions may be the common result of various pathophysiological disturbances (7). One mechanism related to CarAC is that CarAC induces hyalinization, tortuosity, and elongation of vessels in the periventricular white matter. This may cause a decrease in blood flow in the periventricular white matter, which is vulnerable due to marginal perfusion under physiological circumstances (31). Hougaku et al. (32) suggested that the evaluation of CarAC as a proxy for systemic atherosclerosis could predict latent damage to the brain because the progression of arteriosclerotic change in brain was paralleled by systemic atherosclerosis. There is controversy about the validity of CarAC for the risk of silent cerebrovascular lesion or CVD. Shaalan et al. (33) reported that symptomatic plaques are less calcified and more inflamed than asymptomatic plaques and Fanning et al. (34) suggested that the degree of CarAC does not independently predict future stroke risk. Nevertheless, many researchers have suggested that CarAC is one of the vascular risk factors. Arterial calcification occurs during the atherosclerotic process; after all, CarAC may potentially relate to all parameters for the development of CVD (35, 36). Cohen et al. (37) explained three reasons why CarAC appears to carry poor cerebrovascular prognosis: CarAC presents a sign of underlying significant carotid stenosis, CarAC represents simply another indication of a heavy risk factor burden, and CarAC presents an independent risk factor for CVD. The clinical meaning of CarAC and its exact correlation with silent cerebrovascular lesions could not be concluded from this study because there are many confounding and different factors for development of CVD.

There are known biological mechanisms for the association between OSA and silent cerebrovascular lesions during hypoxia, hypercapnia and arousal associated with respiratory events (28, 38, 39). These mechanisms cause inadequate protection of the brain from rapid

fluctuations in pressure that are associated with apnea and long-term damage of cerebral blood vessels (39). With the principle, CarACS may be higher in proportion to the severity of OSA and may be correlated with silent cerebrovascular lesions through CarAC unintentionally found in upper airway CT aside from other examinations including brain MRI.

In this study, several limitations should be acknowledged. First, the study is based on a single medical center, so the number of subjects was relatively small and the proportions of patients in each of the OSA severity, CarAC, and PVH groups were not so even, which may affect the statistical results. Patients who underwent MRI had some limitation for representativity, but they were still consecutive patients and were enrolled without any other exclusion. Second, the brain MRI and airway CT were not performed concurrently because this study is a retrospective study. Third, there were some borderline lesions that were difficult to score with our PVH group definitions for silent cerebrovascular lesions on brain MRI. In some cases, it was difficult to determine the PVH grade, with two observers discussing any discrepancies. However, our study shows very good agreement between radiologists for the grading of PVH (ICC = 0.961). Fourth, we did not sufficiently evaluate the duration or treatment status of OSA, as there was limited information about treatment for OSA in the medical records.

In conclusion, CarAC was an independent risk factor for silent cerebrovascular lesions in patients with OSA. This result may be important for managing co-morbid risk factors for atherosclerosis, to prevent CVD in patients with OSA when high CarACS is incidentally found in airway CT taken for various clinical reasons. The additional analysis of CarACS on OSA patients can be thought to provide more information on their cerebrovascular status.

#### Author Contributions

Conceptualization, K.E., K.M.S., B.W.Y., C.J.H.; data curation, K.M.S., K.E., K.D.Y.; formal analysis, K.E., K.M.S.; investigation, K.M.S., K.E., K.D.Y., B.W.Y., K.C.H.; methodology, K.E., B.W.Y., K.M.S.; project administration, K.E., K.M.S.; resources, K.E., B.W.Y., K.C.H.; software, K.S., K.E., L.K.; supervision, L.K.; validation, K.M.S., K.E.; visualization, K.M.S.; writing—original draft, K.M.S.; and writing—review & editing, K.J.K., K.C.H., C.J.H.

#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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#### REFERENCES

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev* 2017;34:70-81
2. Dong R, Dong Z, Liu H, Shi F, Du J. Prevalence, risk factors, outcomes, and treatment of obstructive sleep apnea in patients with cerebrovascular disease: a systemic review. *J Stroke Cerebrovasc Dis* 2018;27:1471-1480
3. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122:352-360
4. Beaudin AE, Waltz X, Hanly PJ, Poulin MJ. Impact of obstructive sleep apnoea and intermittent hypoxia on cardiovascular and cerebrovascular regulation. *Exp Physiol* 2017;102:743-763
5. Munoz R, Duran-Cantolla J, Martínez-Vila E, Gallego J, Rubio R, Aizpuru F, et al. Severe sleep apnea and risk

of ischemic stroke in the elderly. *Stroke* 2006;37:2317-2321

6. Vermeer SE, Hollander M, Van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003;34:1126-1129
7. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, et al. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017;48:e44-e71
8. Robbins J, Redline S, Ervin A, Walsleben JA, Ding J, Nieto FJ. Associations of sleep-disordered breathing and cerebral changes on MRI. *J Clin Sleep Med* 2005;1:159-165
9. Kim H, Yun CH, Thomas RJ, Lee SH, Seo HS, Cho ER, et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. *Sleep* 2013;36:709-715
10. Nishibayashi M, Miyamoto M, Miyamoto T, Suzuki K, Hirata K. Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. *J Clin Sleep Med* 2008;4:242-247
11. Chousangsunton K, Bhongmakapat T, Apirakittikul N, Sungkarat W, Supakul N, Laothamatas J. Computed tomography characterization and comparison with polysomnography for obstructive sleep apnea evaluation. *J Oral Maxillofac Surg* 2018;76:854-872
12. Tsuda H, Almeida FR, Tsuda T, Moritsuchi Y, Lowe AA. Cephalometric calcified carotid artery atheromas in patients with obstructive sleep apnea. *Sleep Breath* 2010;14:365-370
13. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-832
14. Mahabadi AA, Möhlenkamp S, Lehmann N, Kalsch H, Dykun I, Pundt N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. *JACC Cardiovasc Imaging* 2017;10:143-153
15. Denzel C, Lell M, Maak M, Höckl M, Balzer K, Müller KM, et al. Carotid artery calcium: accuracy of a calcium score by computed tomography-an in vitro study with comparison to sonography and histology. *Eur J Vasc Endovasc Surg* 2004;28:214-220
16. Miralles M, Merino J, Busto M, Perich X, Barranco C, Vidal-Barraquer F. Quantification and characterization of carotid calcium with multi-detector CT-angiography. *Eur J Vasc Endovasc Surg* 2006;32:561-567
17. Koh TK, Kang EJ, Bae WY, Kim SW, Kim CH, Koo SK, et al. Quantitative analysis of carotid arterial calcification using airway CT in obstructive sleep apnea. *Auris Nasus Larynx* 2018 Dec 6 [Epub]. Available at: <https://doi.org/10.1016/j.anl.2018.11.015>
18. Bos D, Ikram MA, Elias-Smale SE, Krestin GP, Hofman A, Witteman JC, et al. Calcification in major vessel beds relates to vascular brain disease. *Arterioscler Thromb Vasc Biol* 2011;31:2331-2337
19. Fukuda H, Kobayashi S, Okada K, Tsunematsu T. Frontal white matter lesions and dementia in lacunar infarction. *Stroke* 1990;21:1143-1149
20. Fukuda H, Kitani M. Differences between treated and untreated hypertensive subjects in the extent of periventricular hyperintensities observed on brain MRI. *Stroke* 1995;26:1593-1597
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545
22. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnoea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034-2041
23. Lui MM, Sau-Man M. OSA and atherosclerosis. *J Thorac Dis* 2012;4:164-172
24. Davies CW, Crosby JH, Mullins RL, Traill ZC, Anslow P, Davies RJ, et al. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep* 2001;24:715-720
25. Kiernan TE, Capampangan DJ, Hickey MG, Pearce LA, Aguilar MI. Sleep apnea and white matter disease in hypertensive patients: a case series. *Neurologist* 2011;17:289-291
26. Gunbatar H, Bulut MD, Ekin S, Sertogullarindan B, Bora A, Yavuz A, et al. A silent pre-stroke damage: obstructive sleep apnea syndrome. *Int J Clin Exp Med* 2016;9:3481-3488
27. Jennum P, Børgesen SE. Intracranial pressure and obstructive sleep apnea. *Chest* 1989;95:279-283
28. Klingelhöfer J, Hajak G, Sander D, Schulz-Varzegi M, Rüther E, Conrad B. Assessment of intracranial hemodynamics in sleep apnea syndrome. *Stroke* 1992;23:1427-1433
29. Patel SK, Hanly PJ, Smith EE, Chan W, Coutts SB. Nocturnal hypoxemia is associated with white matter hy-

perintensities in patients with a minor stroke or transient ischemic attack. *J Clin Sleep Med* 2015;11:1417-1424

30. Zuurbier LA, Vernooij MW, Luik AI, Kocavska D, Hofman A, Whitmore H, et al. Apnea-hypopnea index, nocturnal arousals, oxygen desaturation and structural brain changes: a population-based study. *Neurobiol Sleep Circadian Rhythms* 2016;1:1-7
31. De Leeuw FE, De Groot JC, Bots ML, Witteman JC, Oudkerk M, Hofman A. Carotid atherosclerosis and cerebral white matter lesions in a population based magnetic resonance imaging study. *J Neurol* 2000;247:291-296
32. Hougaku H, Matsumoto M, Handa N, Maeda H, Itoh T, Tsukamoto Y, et al. Asymptomatic carotid lesions and silent cerebral infarction. *Stroke* 1994;25:566-570
33. Shaalan WE, Cheng H, Gewertz B, McKinsey JF, Schwartz LB, Katz D, et al. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. *J Vasc Surg* 2004;40:262-269
34. Fanning NF, Walters TD, Fox AJ, Symons SP. Association between calcification of the cervical carotid artery bifurcation and white matter ischemia. *AJNR Am J Neuroradiol* 2006;27:378-383
35. De Weert TT, Cakir H, Rozie S, Cretier S, Meijering E, Dippel DW, et al. Intracranial internal carotid artery calcifications: association with vascular risk factors and ischemic cerebrovascular disease. *AJNR Am J Neuroradiol* 2009;30:177-184
36. Bos D, Van der Rijk MJ, Geeraedts TE, Hofman A, Krestin GP, Witteman JC, et al. Intracranial carotid artery atherosclerosis: prevalence and risk factors in the general population. *Stroke* 2012;43:1878-1884
37. Cohen SN, Friedlander AH, Jolly DA, Date L. Carotid calcification on panoramic radiographs: an important marker for vascular risk. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;94:510-514
38. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003;290:1906-1914
39. Mohsenin V, Culebras A. Sleep-related breathing disorders and risk of stroke editorial comment: balancing sleep and breathing. *Stroke* 2001;32:1271-1278



## 수면무호흡증 환자에서 경동맥 석회화 점수와 무증상 뇌혈관병변에 대한 상관관계: 상기도 단층촬영 검사와 뇌 자기공명영상을 이용한 연구

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**목적** 수면 무호흡증 환자에서 경동맥 석회화 점수와 무증상 뇌혈관병변의 관계에 대하여 연구하고자 하였다.

**대상과 방법** 본 연구는 후향적 연구로 상기도 단층촬영 및 뇌 자기공명영상을 모두 시행한 60명의 수면무호흡증 환자를 대상으로 선정하였다. 수면다원검사와 관련해서 무호흡 지수 같은 여러 지표들을 이용하여 수면무호흡증과 무증상 뇌혈관 병변과의 관계를 평가하였다. 아가스톤 수치(modified Agarston score method)를 이용해 상기도 단층촬영 내 경동맥 석회화 점수(carotid arterial calcium score; 이하 CarACS)를 측정하였다. 뇌 자기공명영상을 통해 뇌실주위 고신호강도(periventricular hyperintensity; 이하 PVH)를 평가하였다. 나이를 포함한 다양한 임상적 특성을 분석하였다.

**결과** 각각의 PVH grade에 따른 환자의 수는 다음과 같다: grade 0 = 26 (43.3%); grade 1 = 14 (23.3%); grade 2 = 14 (23.3%); grade 3 = 4 (6.7%); grade 4 = 2 (3.3%). 평균 나이, 고혈압, 흡연, 무호흡 지수, CarACS PVH 군들 사이에 의미 있는 차이를 보였다( $p < 0.05$ ). 단변량 회귀 모델에서 CarAC 유무( $\beta = 0.483, p < 0.01$ ), CarACS [ $\beta = 0.482, p < 0.01$ , 그리고 나이( $\beta = 0.360, p = 0.01$ )]가 PVH 군들과 유의미한 상관관계를 보였다. 무호흡 지수와 최저 산소포화도가 PVH 군들과 통계적으로 약한 상관관계를 보였다(각각,  $\beta = 0.267, p < 0.01$ ,  $\beta = -0.219, p = 0.14$ ). 다변량 회귀 모델에서는 CarACS만이 PVH 군들과 유의한 상관관계를 보였다( $p = 0.04$ ).

**결론** CarACS가 수면무호흡증 환자에서 뇌혈관 질환 발생에 대한 독립적인 위험 요소로 작용하였다. 따라서 상기도 단층촬영에서 추가적인 CarACS 분석이 뇌혈관 질환 발생을 예측하는데 유용할 것으로 사료된다.

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