

Full Length Research Paper

Additive effects of obstructive sleep apnea syndrome and hypertension on inflammatory reaction

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Both obstructive sleep apnea syndrome (OSAS) and hypertension are risk factors for cardiovascular diseases. New study showed that arteriosclerosis in OSAS patients with hypertension (HT) is much severe than those patients with only HT or only OSAS. We assume that inflammatory reaction is involved in the pathogenesis in aggravation of arteriosclerosis of OSAS patients with HT. Based on apnea hypopnea index (AHI), 118 persons were divided into four groups: OSAS+HT group (n=58), HT group(n=20), OSAS group (n=20) and control group (n=20). Full polysomnography (PSG) monitoring was performed in all the patients. The serum level of IL-6(interleukin-6), sCD40L, hsCRP (high-sensitivity C-reactive protein), sICAM-1 (soluble intercellular adhesion molecule-1), and VCAM-1 (vascular cell adhesion molecule-1) were detected by enzyme linked immunosorbent assay (ELISA). The serum level of IL-6, sCD40L, hsCRP, sICAM-1, VCAM-1 of the OSAS+HT group was higher than that of the OSAS, HT and the control group (P < 0.05). The serum level of the above-mentioned inflammatory factors of OSAS or HT groups was higher than those of the control group. The serum level of hsCRP, sICAM-1, and VCAM-1 was positively related with AHI and the degree of oxygen desaturation. Inflammatory reaction participate in the pathogenesis of hypertension and OSAS. Inflammatory reaction was aggravated in hypertension patients with OSAS.

Key words: Hypertension, arteriosclerosis, obstructive sleep apnea syndrome, risk, inflammatory processes.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common disorder that affects both children and adults. The morbidity among middle age men is 4 to 9%, and 1 to 2% in middle age women (Young et al., 1993; 2002). It was proved in studies about dynamics of OSAS patients that hypertension happens in 40 to 70% of the studied population (Phillips and Cistulli, 2006) which is much higher than the general population. Furthermore, the risk of hypertension has a positive correlation with the severity of OSAS (Tilkian et al., 1976; Mohsenin et al., 2009). Studies of randomized samples obtained from the general population suggest that the existence of OSAS constitutes a significant risk for vascular diseases independent of other known risk factors (Grote et al., 2000; Shahar et al., 2001; Visser et al., 1999; Marin et al., 2005; Yaggi et al., 2005). Inflammatory processes

associated with OSAS may act as potential mediators of cardiovascular morbidity for these patients (Vgontzas et al., 1997). The neuroendocrine system and vascular endothelial system may be damaged by both hypoxia and inflammatory factors, which lead to dysfunction. Hypertension is also a risk factor of arteriosclerosis. Inflammation reaction is one of the mechanisms. New study showed that arteriosclerosis in OSAS patients with hypertension (HT) is much more severe than in those patients with only HT or only OSAS (Drager et al., 2009). Therefore, the aim of the current study was to evaluate the role of the inflammatory factors in patients suffering from both hypertension and OSAS.

MATERIALS AND METHODS

All patients and controlled subjects were from the outpatients in Xuan Wu Hospital' health examination department from January 2007 to March 2008. The study was approved by the Institutional Ethics Committee, and was performed in accordance with the

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Table 1. Baseline characteristics of the study population.

Variable	OSAS+ HT group (n=58)	HT group (n=20)	OSAS group (n=20)	Control group (n=20)	p
Male/female	34/24	10/10	11/9	10/10	0.71
Age(year)	46.6±7.4	48.7±6.3	41.2±5.2	43.5±8.3	0.36
smoking	21(36.2%)	8(40%)	7(35%)	9(45%)	0.90
Often do exercise	12(20.7%)	3(15%)	5(25%)	4(20%)	0.89
SBP (mmHg)	155.4±12.5	151.2±10.5	131.3±6.8	125.6±7.5	0.03
DBP(mmHg)	102.7±7.6	104.4±8.4	76.6±6.0	74.3±5.8	0.03
BMI (kg/m ²)	27.8±3.2	27.2±1.9	28.3±2.8	26.1±2.4	0.41
FBG (mmol/L)	4.8±1.7	4.6±1.6	5.0±1.4	4.3±1.1	0.46
LDL-c (mmol/L)	3.2±1.0	2.4±1.4	2.5±0.9	2.6±0.5	0.28
AHI (events/h)	45.5±8.7	3.6±1.3	48.8±10.2	-	0.01
Mean SaO ₂ (%)	88.2±5.3	96.4±2.1	86.7±3.9	-	0.03

AHI, apnea/hypopnea index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; LDL-c, low density lipoprotein cholesterol; SaO₂, arterial blood oxygen saturation; Often do exercise, exercise more than twice a week and more than 30 min every once.

guidelines of the Declaration of Helsinki. Exclusion criteria were as follows: 1) chronic or recent (≤ 1 month) clinically significant infectious or inflammatory condition including asthma, trauma, vaccination, any invasive medical/surgical (≤ 3 months) or dental (≤ 1 month) procedure; 2) recent use (≤ 1 month) of anti-inflammatory or antibiotic drugs; 3) active smoker; 4) coexistence of chronic obstructive pulmonary diseases, IHD, diabetes, hyperlipidaemia, cerebrovascular disease or chronic renal disease; 5) inability to perform test. Patients with sleep disorders such as upper airway resistance syndrome, central sleep apnea syndrome, and periodic limbs movement narcolepsy were also excluded.

Full polysomnography (PSG) monitoring was performed in all the three patient groups except the healthy control group with the Embla-Monet 32 Sleep System (Embla, USA) in Sleep Clinic of Xuan Wu Hospital. Electroencephalography, electrooculography, electromyography and electrocardiography were performed simultaneously. Ventilator flow at the nose and mouth was measured.

Ventilation movements of the chest and abdomen were monitored by inductive plethysmometric bands. The arterial oxygen saturation (SaO₂) was measured transcutaneously with fingertip pulse oximetry. American Academy of Sleep Medicine (AASM) manual 2007 for the scoring of sleep and associated events was used (Iber et al., 2007): Apnea was defined as complete cessation of airflow for at least 10 s, associated with oxygen desaturation of 3%. The AASM scoring manual provides two acceptable definitions for hypopnea: a recommended one that requires a $\geq 30\%$ decline in nasal-pressure-transducer signal excursions with a $\geq 4\%$ desaturation from pre-event baseline, and an alternative option that requires a $\geq 50\%$ decline in nasal-pressure-transducer signal excursions with a $\geq 3\%$ desaturation or arousal. The summation of obstructive apneic events and hypopneic events per hour of sleep was obstructive apnea-hypopnea index (AHI). The AHI cutoffs for mild, moderate and severe OSA were 5 to 14.9, 15 to 29.9, and ≥ 30 events per hour of sleep, respectively. PSG was started at 10 pm and ended at 6 am and special staff technicians performed data processing. 24 h blood pressure was monitored by blood pressure monitors (90217-1B, Space Lab, USA), and mean ABP was recorded. In our primarily study, we found that inflammation factors in mild OSAS patient did not raise up as significant as in moderate and severe OSAS patients. 78 moderate or severe OSAS patients were included by PSG in sleep clinic. 20 hypertension patients and 20 healthy people were included into this study. They were divided into four groups (the baseline characteristics of the study population

are shown in Table 1): 1) OSAS+ HT group: patients with moderate or severe OSAS (AHI ≥ 15 /h) and hypertension (BP $\geq 140/90$ mmHg) (n = 58) (moderate OSAS 28 people, severe OSAS 30 people); 2) HT group: patients with hypertension (BP $\geq 140/90$ mmHg) (n = 20); 3) OSAS group, moderate or severe OSAS (AHI ≥ 15 /h) (n=20) (moderate OSAS 9 people, severe OSAS 11 people); 4) normal control group: healthy person with neither OSAS nor hypertension (n=20).

No significant differences were detected among the four groups with respect to age and baseline body mass index (BMI) (p>0.05).

Biochemical analysis

The morning after PSG monitoring, when the patients woke up spontaneously, the blood samples were collected, and serum was extracted and store in -80°C until assayed. Detection of serum total IL-6, sCD40L, hsCRP, sICAM-1, and VCAM-1 was performed using the commercially available sandwich ELISA assays (Oncogene Research Products, USA).

Statistical analysis

Data was expressed as mean \pm standard deviation (SD) for continuous variables. Data with Gaussian distribution were processed with analysis of variance and Student-Newman-Keuls test. Nonparametric analysis using the Kruskal-Wallis tests was used for data with variables with non-Gaussian distribution. Correlation was calculated using Spearman's rank correlation test. The significance of differences within two groups was analyzed using the Student *t* test and four groups using variance test. All statistical analyses were carried out using statistical software (SPSS,13.0). A p<0.05 was considered to indicate statistical significance.

RESULTS AND DISCUSSION

The serum level of IL-6, sCD40L, hsCRP, sICAM-1, and VCAM-1 of the OSAS +HT group was higher than those of the OSAS, HT and control groups (p< 0.05). The serum level of IL-6, sCD40L, hsCRP, sICAM-1, VCAM-1

Table 2. Inflammatory factors of each group.

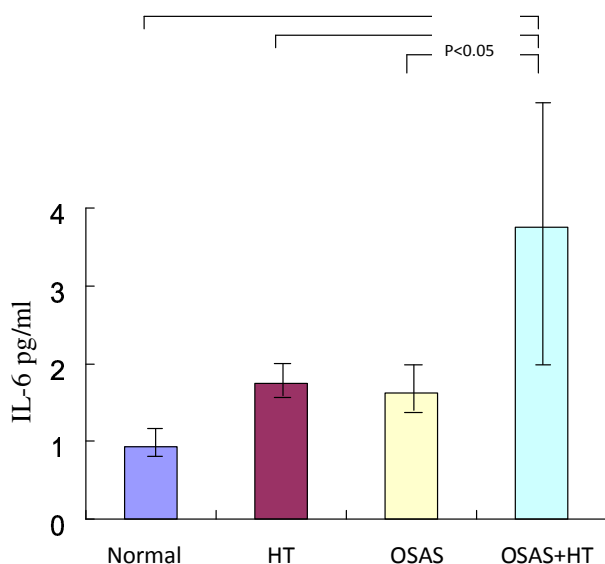
Variable	Control group (n=20)	HT group (n=20)	OSAS group (n=20)	OSAS+ HT group (n=58)	ANOVA P
IL-6 (pg/ml)	0.92±0.34	1.75±0.30	1.62±0.43	3.76±2.80*#¥	0.02
sCD40L (ng/ml)	2796±1046.6	3227.1±1079.7	3551.1±894.2	4842.0±2255.7* #	0.03
hsCRP (ng/ml)	0.68±0.48	2.68±1.47*	1.31±0.62	3.94±2.61*	0.02
VCAM-1(ng/ml)	419.1±171.5	768.9± 83.5*	853.3±112.6*	1569.1±372.2*#¥	0.02
sICAM-1 (ng/ml)	55.3±19.0	96.5± 14.7	118.3±18.3*	390.8± 149.7*#¥	0.01

T test: *Significant difference compared with normal control group ($p<0.05$); #significant difference compared with HT group ($p<0.05$); ¥significant difference compared with OSAS group ($p<0.05$).

Table 3. Correlation coefficient (r value).

Variable	IL-6	CD40L	hsCRP	VCAM-1	sICAM-1
LDL-C	-0.083	-0.251	-0.094	0.110	0.035
GLU	-0.15	-0.33	-0.048	-0.123	-0.049
BMI	0.219	0.302	0.301	0.211	0.348*
AHI	0.153	0.117	0.529**	0.505**	0.816**
Oxygen desaturation	0.150	0.265	0.477**	0.393**	0.570**
MAP	-0.057	0.125	0.432**	-0.061	0.159

* $p<0.05$, ** $p<0.01$.

**Figure 1.** IL-6's contrast in the four groups.

of OSAS and HT groups were higher than those of the control group (Table 2). The serum levels of hsCRP, sICAM-1 and VCAM-1 are positively related with AHI and the degree of oxygen desaturation. The hsCRP has positive correlation with MAP. The serum level of sICAM-1 is positively related with BMI. The above inflammatory factors did not have any correlation with blood glucose or

low density lipoprotein cholesterol (LDL) as shown by the correlation analysis results listed in Table 3 and Figures 1 to 6.

Atherosclerosis is the pathology of cardiovascular disease. Hypertension can induce atherosclerosis. Inflammation is one reason for this process. On the other hand, atherosclerosis promotes hypertension. Our study found that serum levels of inflammatory factors in hypertension patients increased significantly than those in the healthy volunteers. Researchers found that inflammatory factors may have been involved in pre-hypertension stage (Chrysohoou et al., 2004). ICAM-1 will increase significantly when the extent of injury of hypertension patients organs increase, which indicates that ICAM does not only participate in the beginning of hypertension, but also relates to severity of hypertension (von Känel et al., 2004). It can be seen that hypertension are closely related to inflammatory reaction.

Cardiovascular disease, especially hypertension, has been associated with OSAS (Gami and Somers, 2004). The Sleep Heart Health Study demonstrated convincingly that OSAS is an independent risk factor for hypertension and all cardiovascular disease (Shahar et al., 2001). OSAS has also been associated with hyper-tension on the basis of animal studies (Brooks et al., 1997) and other large epidemiologic studies (Peppard et al., 2000; Bixler et al., 2000; Nieto et al., 2000).

Wisconsin Cohort Study (WSCS) found that hypertension risks increased significantly in patients with sleep

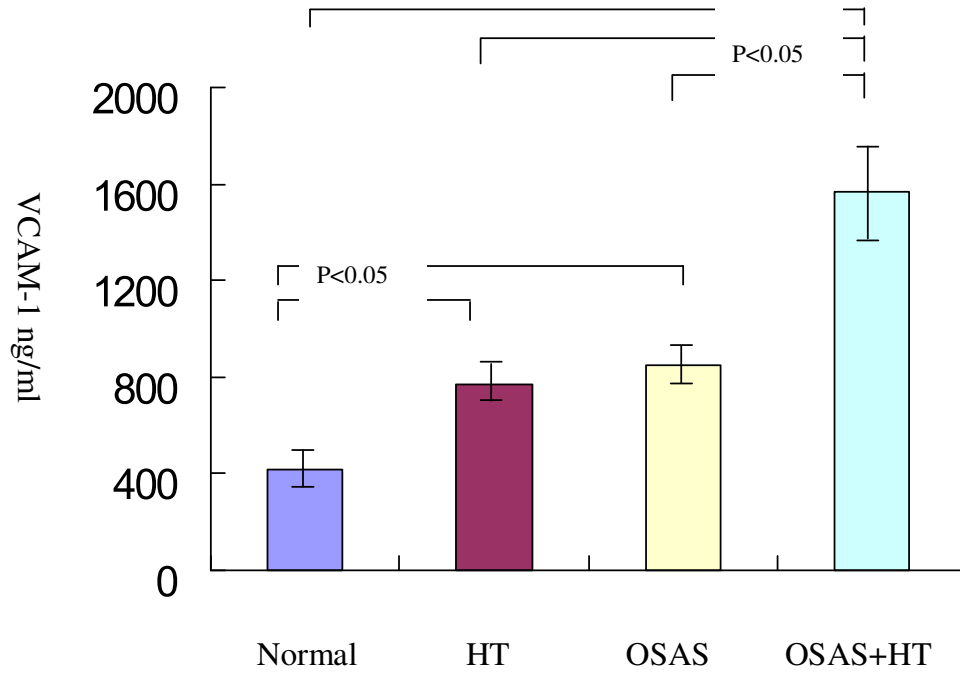


Figure 2. VCAM-1's contrast in four groups

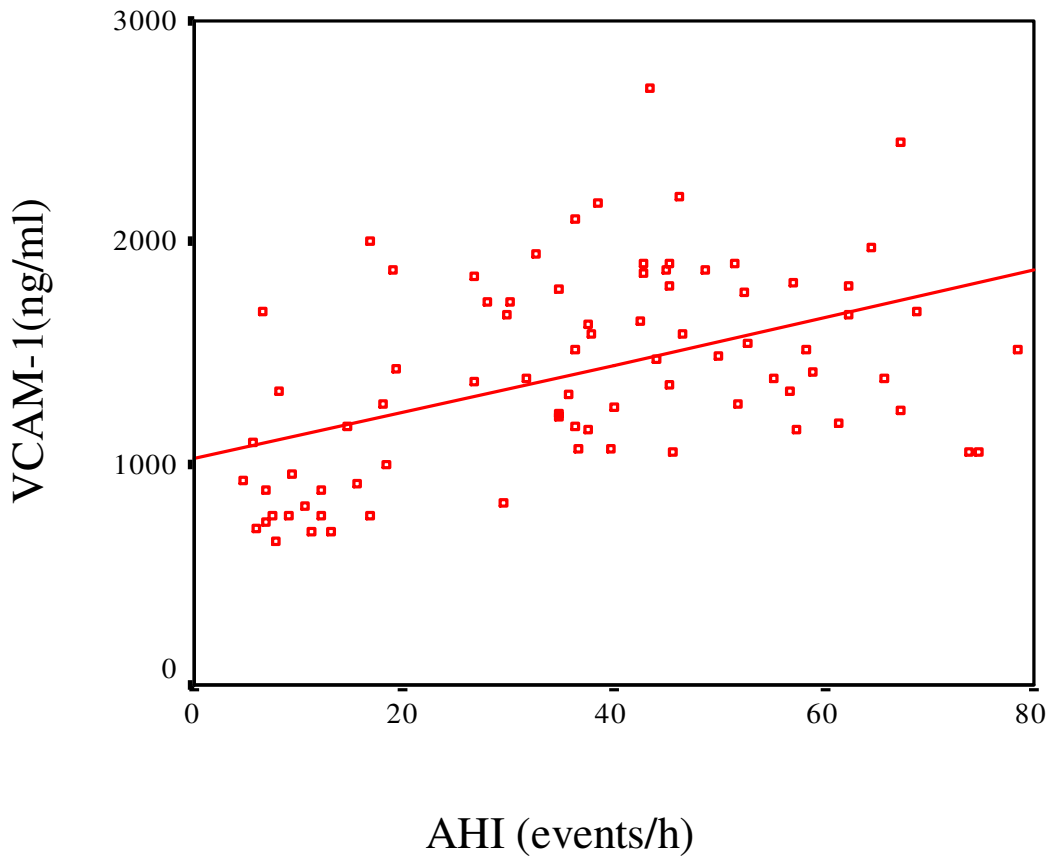


Figure 3. Correlation between VCAM-1 and AHI.

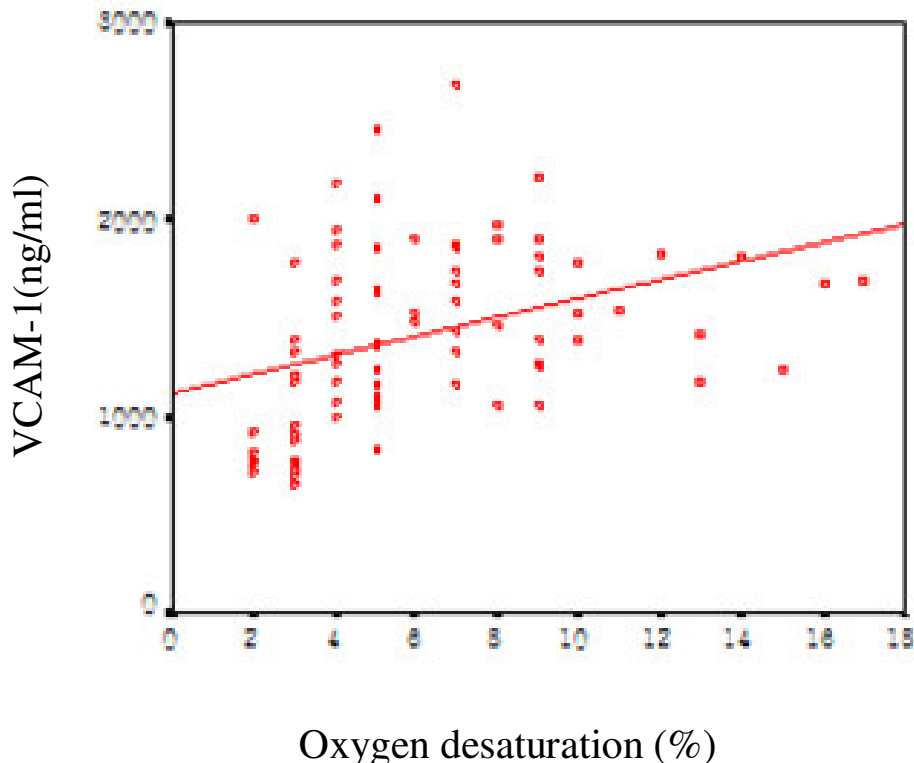


Figure 4. Correlation between VCAM-1 and oxygen desaturation (%).

apnea, and the morbidity had a positive correlation with AHI (Peppard et al., 2000). Another study found that the systolic blood pressure and diastolic blood pressure before and after the OSAS patients slept had a positive correlation with the AHI (Yu et al., 2006).

OSAS has also been associated with an increase in various inflammatory markers associated with the development of atherosclerosis, including C-reactive protein and interleukin-6 (Lavie, 2003). Additionally, OSAS has been associated with endothelial dysfunction, a known precursor to the development of atherosclerosis (Nieto et al., 2004; Kraiczi et al., 2001).

Repeated hypoxia may call up oxidative stress and lead to increasing of reactive oxygen species (ROS) in patients with OSAS. Repeated sleep apnea could cause hypoxia-reoxygenation, and this condition is similar to that of ischemia-reperfusion. This protocol may produce a large amount of ROS. Despite the severity of hypoxia is not as great as that of ischemia-reperfusion, hypoxia-reoxygenation alternation may occur for hundred times one night and last for several years. So a large amount of oxygen free radicals will oxidize low-density lipoprotein and lead to direct or indirect vascular damage. As a consequence, active vascular cells may start releasing all kinds of cell factors, such as IL-1, IL-6, CD40L, TNF- α . These factors could lead to a significant increase of sICAM-1 and VCAM-1 expression in endothelial cells, smooth muscle cells and leucocytes, and increase the

serum level of sICAM-1 and VCAM (Liu et al., 2000; Suematsu et al., 2002). sICAM and VCAM are members of immunoglobulin superfamily, both are transmembrane surface protein antigens. The above antigens spread widely on tissue surface, and induced inflammatory reaction between leucocytes and endothelial cells (Golias et al., 2007). The increased ROS may trigger expression of pro-inflammatory genes (Dyugovskaya et al., 2002).

Study of OSAS patients' surgery result proved that after improving patients' ventilation, the serum level of IL-6, TNF- α and hsCRP decreased too. This proved that hypoxia may cause inflammatory reaction (Constantinidis et al., 2008). Our study also proved that OSAS patients' Hs-CRP, VCAM-1 and sICAM-1 levels had positive correlation with AHI. The inflammatory mediators induce inflammatory cells such as mast cell and macrophage adhere to the vascular endothelium, which cause inflammatory reaction and damage to endothelium. Dysfunction of vascular endothelium included endothelium-dependent decreasing of vascular dilating function and increasing of vascular constricting function. The reactions mentioned above may be part of the mechanisms for OSAS which lead to atherosclerosis. So, the OSAS is a risk factor of cardiovascular disease.

Our study prompted that serum levels of various inflammatory factors were higher in OSAS and hypertension patients compared with patients only with hypertension or OSAS. This result highly suggests that inflammatory

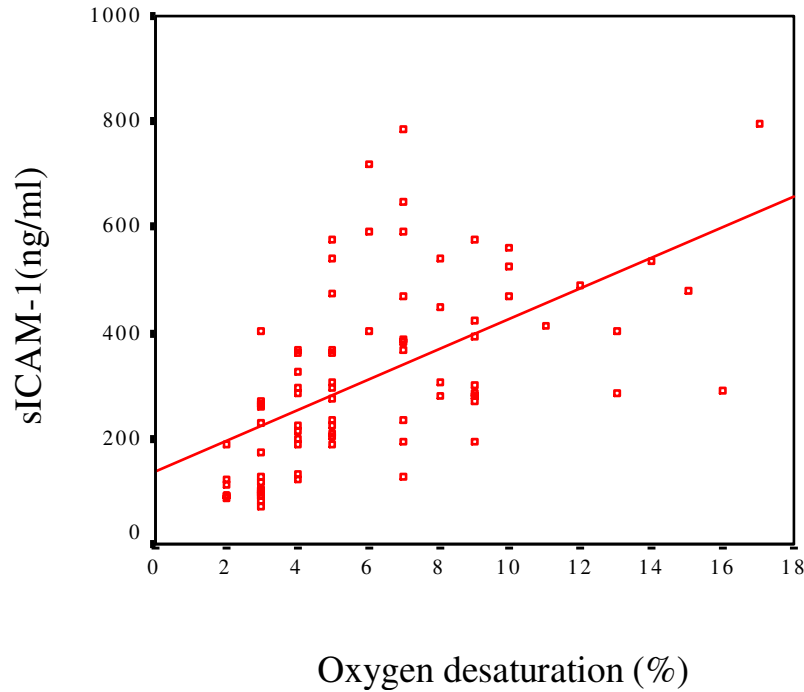


Figure 5. Correlation between VCAM-1 and oxygen desaturation (%).

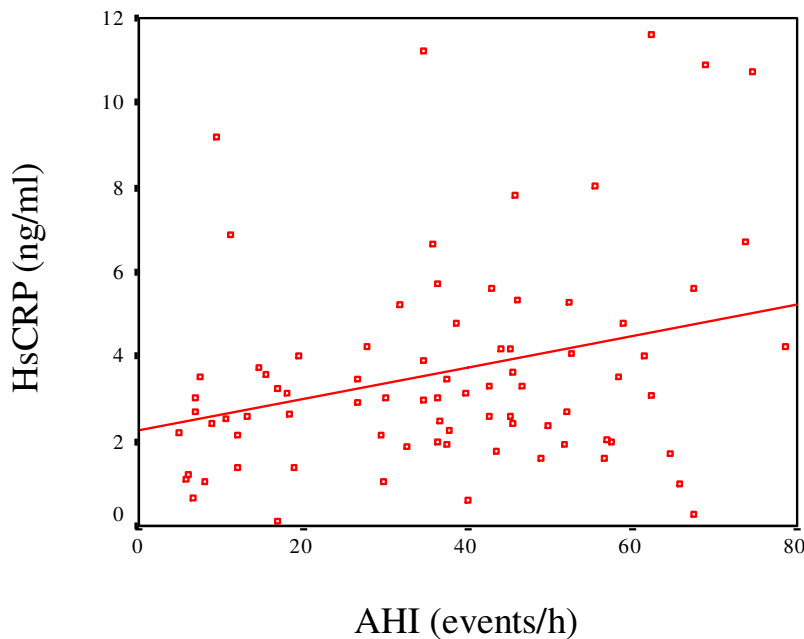


Figure 6. Correlation between hsCRP and AHI.

reaction may be congenerous. Atherosclerosis promotes higher blood pressure, and higher blood pressure makes faster progression of atherosclerosis. This prompted the seriousness of atherosclerosis in patients with OSAS and HT. This study also proved that OSAS patients accompanied by hypertension had higher inflammatory

factors, which induced more serious impairment of vascular endothelium. These differences indicated that inflammatory reactions were more severe in this kind of patients. Thus, hypertension patients who suffer from OSAS may be more prone to cardiocerebral vascular disease.

Conclusions

This study found that serum level of inflammatory factors for patients with OSAS or hypertension conditions were significantly increased than that of the healthy volunteers. In the study, the serum level of IL-6, sCD40L, hsCRP, ICAM-1, and VCAM-1 of patients with both OSAS and hypertension were significantly higher than those in the patients suffering only OSAS or hypertension. The above results indicate that enhanced inflammatory reaction may be the one reason of aggravated arteriosclerosis in patients with OSAS and hypertension.

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