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High Levels of Inflammation and Insulin Resistance in Obstructive Sleep Apnea Patients with Hypertension

Xiaoshun Qian,[1,3] Tong Yin,[1,2,3] Tianzhi Li,[1] Chunyan Kang,[1] Ruibiao Guo,[1] Baojun Sun,[1] and Changting Liu[1]

Abstracts—Hypertension induced by obstructive sleep apnea (OSA) may be multifactorial in origin, and systemic inflammation is one of the major factors. However, OSA patients do not always have the identical probability with hypertension even in patients with the same history and degree of OSA. The aim of this study was to compare the levels of inflammation and insulin resistance in two groups of patients who had the same degree as well as the same long history of OSA, but with/without hypertension. OSA patients (Apnea Hyponea Index, AHI≥40/h, n=70) were examined by polysomnography and blood analysis for the measurements of fasting plasma glucose, serum insulin (FINS), high-sensitivity C-reactive protein (CRP), peptide C,TNF-α, IL-6, and IL-10. Patients with hypertension (n=40) had higher level of LDL-C and lower HDL-C levels than patients without hypertension. Almost half (16/40) of OSA patients with hypertension had family history of hypertension. Moreover in OSA patients with hypertension, the levels of TNF-α, IL-6, and CRP were higher, but IL-10 was lower than those without hypertension. FINS, peptide C, HOMA-IR, and HOMA-islet were also higher in OSA patients with hypertension. OSA patients with hypertension have higher level of inflammation and insulin resistance. Systemic inflammation and insulin resistance are both important factors for the development of hypertension in OSA patients.

KEY WORDS: obstructive sleep apnea (OSA); hypertension; inflammation; insulin resistance.

INTRODUCTION

Obstructive sleep apnea (OSA) is highly prevalent in the world. In recent years, there has been a large body of work assessing the role of OSA as an independent risk factor for hypertension. Kono *et al.* demonstrated that the percentage of hypertensive patients were significantly higher in the OSA group (45 %) than in the non-OSA group (15 %) [1]. Early diagnosis and treatment of OSA may be beneficial in the management of hypertensive patients, particularly in those with poorly controlled hypertension. Recent study demonstrated that hypertension induced by OSA may be multifactorial in origin, and chronic systemic inflammation was one of the important factors [2]. However, we found that OSA patients do not always had identical probability with hypertension, even with the same OSA degree and the same long OSA history. We suspected some people may be predisposed to hypertension underline OSA.

The purpose of this study was to compare the levels of inflammation and insulin resistance in two groups of OSA patients who had the same OSA degree and long history but with/without hypertension. The differences existed between them were assessed.

Summary at glance OSA patients with hypertension (n=40) have higher level of inflammation and insulin resistance than OSA patients without hypertension (n=30). Systemic inflammation and insulin resistance are both important factors for the development of hypertension in OSA patients.

Xiaoshun Qian and Tong Yin, as co-first authors, contribute equally to this manuscript.

[1] Department of Geriatric Respiratory Disease, General Hospital of People's Liberation Army, No. 28 Fu Xing Road, Beijing, People's Republic of China 100853

[2] Institute of Geriatric Cardiology, General Hospital of People's Liberation Army, No. 28 Fu Xing Road, Beijing, People's Republic of China 100853

[3] To whom correspondence should be addressed at Department of Geriatric Respiratory Disease, General Hospital of People's Liberation Army, No. 28 Fu Xing Road, Beijing, People's Republic of China 100853. E-mail: qianxs@yahoo.com ; yintong2000@yahoo.com

MATERIAL AND METHODS

Subjects

A consecutive male population with clinical symptoms of sleep apnea (n=70), who was examined by polysomnography (PSG) from August 2006 to October 2009 in General Hospital of People's Liberation Army, was divided into two groups according to with/without hypertension. All of them were severe OSA patients (AHI>40/h, SaO_2<80 %) and had the similar OSA courses. The subjects were all Chinese Han ethnic, and no other ethnic group was included. Patients with heart failure, or other respiratory problems including chronic obstructive pulmonary disease, were excluded from the study. Patients with kidney disease and hormonal disease were also excluded. OSA was established on the basis of clinical and polysomnographic criteria. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or the current use of antihypertensive medication. AHI was calculated as the summary measurement of sleep-disordered breathing. Thirty healthy volunteers without clinical symptoms of sleep apnea were recruited in control group. They were examined by PSG and AHI was less than 5/h. The control group matched with OSA patients in age, but BMI was lower. The study protocol was approved by the Research Ethics Committee of General Hospital of People's Liberation Army, and all patients gave their informed consent before study commencement.

PSG

Overnight PSG (Compumedics, Melbourne, Australia) was performed between 22:00 pm–06:00 am. The PSG consisted of continuous polygraphic recording from surface leads for electroencephalography, electrooculography, electromyography, electrocardiography, thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry for oxyhemoglobin concentration, tracheal microphone for snoring and sensor for the position during sleep. PSG records were staged manually according to standard criteria. Severity of OSA was determined by the AHI and lowest oxygen saturation during sleep (lowest SaO_2).

Laboratory Examinations

Venous blood was obtained in the fasting state at 7:00 am after overnight PSG to measure fasting plasma glucose (FPG), serum insulin (FINS), high-sensitivity C-reactive protein (CRP), and peptide C using a fully automatic biochemical device (Simens Dimension RLMax). TNF-α, IL-6, and IL-10 were measured with ELISA method. Insulin resistance index was estimated using the homeostasis model assessment ratio (HOMA-IR) [fasting serum insulin (milliunits per liter)×FPG (millimoles per liter)/22.5] and HOMA-islet [20×FINS/(FPG-3.5)].

Statistics Methods

The results were expressed as means±standard errors. The Student's t test was used to compare age, BMI, serum parameters, and sleep respiratory parameters in OSA patients with or without hypertension. Proportions were compared by the chi-squared test and p values less than 0.05 were considered to be statistically significant.

RESULTS

Clinical Characteristics of Control Group and OSA Patients

Baseline characteristics of the study population are shown in Table 1. LDL-C was higher but HDL-C was lower in the group of OSA with hypertension. OSA patients with hypertension had more (16/40) family history of hypertension than OSA without hypertension (7/30). Age, BMI, ESS, RDI, apnea time, and oxygen saturation did not differ significantly between the two groups. Statistical analysis was not performed on type 2 diabetes due to the small number of samples although more type 2 diabetes was in OSA with hypertension group.

Levels of Inflammation of OSA Patients in Two Groups

Levels of serum TNF-α, IL-6, and IL-10 are shown in Table 2. Serum TNF-α and IL-6 were higher but IL-10 was lower in OSA patients with hypertension compared to OSA patients without hypertension. Moreover serum IL-10 in OSA patients was also lower than control group. CRP was the highest in OSA with hypertension and it was also higher in OSA patients without hypertension than control group.

Table 1. Characteristics of OSA patients and controls

	Control group	OSA without hypertension	OSA with hypertension
n	40	30	40
Age (years)	46.3±8.1	45.0±9.0	46.9±7.0
BMI (kg/m^2)	24.1±2.3	29.4±2.1*	28.2±2.5*
ESS	–	13.2±4.1	13.6±4.0
Family history of hypertension	8	7	16$^{*, ***}$
With type 2 diabetes	1	1	4
HDL-C (mmol/L)	0.97±0.21	0.95±0.18	0.85±0.19$^{*, ***}$
LDL-C(mmol/L)	2.69±0.83	2.71±0.89	3.24±0.86$^{*, ***}$
Course of OSA (years)	–	11.2±4.0	10.8±4.5
RDI	2.5±2.3	57.5±16.3**	54.2±15.4**
Longest apnea time	11.2±1.2	79.4±18.2**	71.5±20.4**
Mean apnea time	10.9±0.8	29.9±6.2**	29.1±6.8**
Lowest oxygen saturation (%)	93.6±1.3	66.9±8.7**	68.1±8.0**
Average oxygen saturation (%)	94.8±0.5	89.6±6.2**	91.4±3.1**

BMI body mass index, *ESS* Epworth sleepiness scale, *RDI* respiratory disorder index
* $P<0.05$ *vs* control groups; ** $P<0.01$ *vs* control groups; *** $P<0.05$ vs OSA without hypertension groups

Serum peptide C, FINS, FPG, HOMA-IR, and HOMA-Islet Levels in Two Groups

Serum peptide C, FINS, FPG, HOMA-IR, and HOMA-islet levels are shown in Table 3. Serum true insulin, peptide C, FPG, HOMA-IR, and HOMA-islet were higher in OSA patients with hypertension than those without hypertension.

DISCUSSION

OSA is a chronic condition characterized by repetitive upper airway collapse during sleep, causing intermittent hypoxemia. It could provoke oxidative stress and systemic inflammation, and impair vascular endothelial function. OSA is increasingly recognized to be an independent cardiovascular risk factor [3]. Large epidemiologic studies have established that OSA is a risk factor for developing hypertension [4]. Approximately half of the patients with sleep apnea may have underlying hypertension. In a subgroup analysis of the Sleep Heart Health Study, patients<60 years of age with sleep apnea were more likely to demonstrate a significant relationship between minimum oxygen saturation and the development of hypertension [5]. Patients with sleep apnea exhibit greater HDL dysfunction and oxidized LDL levels compared to matched controls. Of note, AHI explained 30 % of the variance in HDL dysfunction in sleep apnea [6]. In our study, we found patients with OSA may not be same susceptible to consequent hypertension even they have same degree of AHI and minimum oxygen saturation. Almost half of OSA patients with hypertension had family history of hypertension, and they also have higher LDL-C and lower HDL-C in serum.

OSA has been associated with a range of cardiovascular diseases, and it has been etiologically linked most convincingly to hypertension. Hypertension induced by OSA may be multifactorial in origin and may include systemic inflammation, oxidative stress, endogenous vasoactive factors, endothelial dysfunction, increased sympathetic activation, and metabolic dysregulation [2]. Systemic inflammation is one of important origins. OSA patients experience repetitive short cycles of oxygen desaturation followed by rapid

Table 2. Levels of serum TNF-α, IL-6, IL-10, and CRP(x±SD)

	n	TNF-α (ng/mL)	IL-6 (pg/mL)	IL-10 (ng/mL)	CRP (ng/mL)
Control group	40	1.14±0.40	88.85±41.48	38.60±10.60	0.18±0.12
OSA without hypertension	30	1.15±0.37	89.56±36.19	26.11±20.98*	0.28±0.11*
OSA with hypertension	40	1.29±0.22*	129.41±36.56**	14.79±9.13$^{*, ***}$	0.40±0.22$^{*, ***}$

* $P<0.05$ *vs* control groups; ** $P<0.01$ *vs* control groups; *** $P<0.05$ *vs* OSA without hypertension group

Table 3. Levels of serum peptide C, FINS, HOMA-IR, and HOMA-islet(x±SD)

	n	FINS (μIU/mL)	peptide C (ng/mL)	FPG (mmol/L)	HOMA-IR	HOMA-islet
Control group	40	5.16±1.43	1.42±0.37	4.88±0.29	1.21±0.32	59.17±21.23
OSA without hypertension	30	10.93±3.14*	2.95±0.84*	5.19±0.64*	2.87±1.16*	134.96±32.61*
OSA with hypertension	40	15.90±7.92**	3.58±1.28**	5.93±1.43**	5.47±4.04**	223.68±173.31**

* $P<0.05$ *vs* control group; ** $P<0.05$ *vs* OSA without hypertension group

reoxygenation in their sleep [6]. This intermittent hypoxia may promote activation of various inflammatory cells, particularly lymphocytes and monocytes, which increase the levels of inflammatory factors including TNF-α, IL-6 and CRP, and decrease anti-inflammatory factors, *i.e.* IL-10. Recent study found that systemic inflammatory processes play an important role in the pathogenesis of hypertension, and circulating inflammatory factors have been associated with hypertension. TNF-α stimulates the production of endothelin-1 and angiotensinogen [7, 8]. Serum TNF-α concentration has been reported to be positively correlated with systolic blood pressure and insulin resistance in humans [9], and increased TNF-α secretion has been observed in monocytes from hypertensive patients [10]. IL-6 is a multifunctional cytokine which mediates inflammatory responses. IL-6 stimulates the central nervous system and sympathetic nervous system, which may result in hypertension [11, 12]. IL-6 can induce an increase in plasma angiotensinogen and angiotensin II [13], leading to development of hypertension. IL-6 also induces CRP production. CRP is a biomarker of systemic inflammation which plays an important role in cardiovascular diseases [14–16]. In a large cohort of snoring children, Tauman R *et al.* found that those with moderate to severe OSA had elevated plasma IL-6 and CRP levels compared to children with mild OSA and controls, and that both plasma IL-6 and CRP levels were significantly correlated with OSA severity [17]. IL-10 is a pleiotropic cytokine and inhibits a broad array of pro-inflammatory immune responses [16–18]. IL-10 expression was negatively correlated with the severity of OSA [19] and exogenous IL-10 can normalize blood pressure and endothelial function [20]. In this study, OSA patients with hypertension have higher levels of inflammatory factors (TNF-α, IL-6, and CRP) and lower levels of anti-inflammatory factors (IL-10). Our findings demonstrate that systemic inflammation is not identical in severe OSA patients and OSA patients with hypertension have higher levels of inflammation than those without hypertension. Our study reinforced the concept that systemic inflammation is one of important original factors and may be etiologically linked most convincingly to hypertension.

Obesity is thought to be centrally involved in increasing the clinical risk of metabolic and cardiovascular diseases [21]. Adipose tissue is now known to be an active endocrine organ that produces a variety of pro-inflammatory cytokines including IL-6 and TNF-α [22]. In our study, BMI and inflammatory mediators in OSA patients were higher than control group and obesity may have some effects in chronic inflammation of OSA patient. Moreover, inflammatory level in OSA patients with hypertension was higher than OSA patients without hypertension and it suggested hypoxia and reoxygenation in sleep may have important role in chronic inflammation of OSA patients with hypertension and the responses of OSA patients to hypoxia were not all identical.

It has been demonstrated that insulin resistance is associated with a state of chronic low-grade inflammation. Increased release of TNF-α and IL-6 and decreased release of IL-10 have a role in the development of insulin resistance. TNF-α and IL-6 act through classical receptor-mediated processes to stimulate both the c-Jun amino-terminal kinase and the IκB kinase-β/nuclear factor-κB pathways, resulting in upregulation of potential mediators of inflammation that can lead to insulin resistance [23]. In our study, serum true insulin, peptide C, HOMA-IR, and HOMA-islet were higher in OSA patients with hypertension than those without hypertension. It suggested that inflammation may have some effects in developing insulin resistance in OSA patients with hypertension.

Insulin resistance is another cause of hypertension and several mechanisms connect insulin resistance with hypertension. An anti-natriuretic effect of insulin has been established by accumulating data indicating that insulin stimulates renal sodium re-absorption [24]. This anti-natriuretic effect is preserved, and may be increased in individuals with insulin resistance, and this effect may play an important role for development of hypertension [25]. Proximal fractional sodium re-absorption was significantly greater in individuals with insulin resis-

tance, as compared with those without insulin resistance [26]. Insulin resistance is also associated with development of salt-sensitive hypertension through the antinatriuretic effect of insulin [27]. Our study showed that biomarkers of insulin resistance were higher in OSA patients with hypertension and demonstrated that insulin resistance has an important role in developing hypertension in OSA patients.

In summary, this study supports the hypothesis that systemic inflammation and insulin resistance are both important factors for the development of hypertension. Moreover, we found severe OSA patients with hypertension have higher level of inflammation and insulin resistance. It suggests that responses of OSA patients to intermittent hypoxemia in sleep were not all identical and the causes are unknown. We presumed that genetic predisposition of OSA patients may be one of important factors.

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Conflict of Interest. No potential conflict of interest relevant to this article was reported.

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