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ORIGINAL ARTICLE

Changes in Plasma Angiotensin II and Circadian Rhythm of Blood Pressure in Hypertensive Patients with Sleep Apnea Syndrome Before and After Treatment

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Objective To explore the changes in plasma angiotensin II (Ang II) and circadian rhythm of blood pressure among hypertensive patients with sleep apnea syndrome (SAS) before and after continuous positive airway pressure (CPAP) or surgical treatment.

Methods A total of 180 essential hypertension patients were enrolled in our study. The determination of plasma Ang II concentration, ambulatory blood pressure (ABP), and polysomnography (PSG) monitoring were performed before and 3 months after CPAP or surgical treatment.

Results Patients were classified into three groups by their apnea-hypopnea index (AHI): essential hypertension group (EH group, $n=72$; $AHI<5$), essential hypertension with mild SAS group (EH+mild SAS group, $n=60$, $5\leq AHI<20$), and essential hypertension with moderate and severe SAS group (EH+moderate-severe SAS group, $n=48$, $AHI\geq 20$). The concentrations of plasma Ang II in the above three groups were 13.42 ± 3.27 , 16.17 ± 3.82 , and 18.73 ± 4.05 ng/mL respectively before treatment, and Ang II concentration in EH patients combined with SAS was significantly higher than that in EH group (all $P<0.05$). After treatment the values in the latter two groups significantly decreased to 14.67 ± 2.56 and 15.03 ± 3.41 ng/mL respectively ($P<0.05$). The incidence of non-dipper blood pressure curve in EH patients was 31.9%, and those in hypertensive patients with mild SAS and moderate-severe SAS were 51.7% and 58.3%, respectively before treatment. The incidence of non-dipper blood pressure curve in the EH patients with mild SAS was significantly higher than that of patients with EH alone ($P<0.05$). After CPAP treatment or surgery, the

incidence of non-dipper blood pressure curve in the two SAS groups was significantly decreased to 38.3% and 39.6%, respectively ($P < 0.05$).

Conclusions Ang II might play a role in blood pressure variability in patients with obstructive SAS. CPAP or surgical treatment can improve blood pressure disorder and decrease plasma Ang II level in patients with obstructive SAS.

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ANGIOTENSIN II (Ang II) is the major active peptide product of the renin-angiotensin-aldosterone system. Under normal circumstances, Ang II has a beneficial effect on the maintenance of blood pressure; but during pathological conditions, too much Ang II can cause strong contractions of blood vessels and hypertension, which result in damage to the heart, brain, and kidney. Ang II has been found to be involved in the occurrence and development of atherosclerosis.¹

There is a strong correlation between sleep apnea syndrome (SAS) and hypertension. Notably, 50%-60% of SAS patients have hypertension and 50% of hypertensive patients have SAS.² SAS is an independent risk factor for hypertension, in addition to age, body mass, diet, smoking history, as well as heart and kidney disease, and other factors.³ In 2003, SAS was rated as the major cause of secondary hypertension by the US Committee of Prevention, Detection, Evaluation and Treatment of High Blood Pressure in its seventh report.⁴

With the use of ambulatory blood pressure monitoring, people have a new understanding of variations in blood pressure throughout the course of a day. Blood pressure is influenced by both environmental and biological factors and shows dynamic changes in the body. The blood pressure of most normal people falls to the lowest value when they sleep at night and increases rapidly in the morning upon waking up, and it typically reaches its peak value within the first few hours of daily activities.⁵ According to the variation of blood pressures at night, blood pressure has been divided into dipper (diurnal blood pressure change ranging from 10% to 20%) and non-dipper forms of hypertension (diurnal blood pressure change being less than 10%).⁶ It is well known that non-dipper blood pressure, a risk factor independent from pressure load, is significantly related to target organ damage.⁵ Non-dippers have been reported to present with greater clinical and subclinical target organ damage compared with dippers.⁷ In this study, we explored the changes in plasma Ang II and circadian rhythms of blood pressure in essential hypertensive patients with SAS before and after treatment, to investigate the mechanism of blood

pressure disorder in essential hypertension patients combined with SAS and find effective treatment.

PATIENTS AND METHODS

Patients

Consecutively hospitalized patients in the Department of Otolaryngology-Head and Neck Surgery of our hospital from January 2006 to June 2009 who fulfilling the essential hypertension diagnostic criteria of the 2003 ISH/WHO guidelines⁸ were enrolled in this study. Patients with secondary hypertension; with serious cardiovascular and cerebrovascular complications, valvular heart disease, or severe liver and kidney dysfunctions, very high-risk Grade 3 hypertension; requiring intravenous antihypertensive medication to control heart failure and aortic dissection caused by high blood pressure were excluded. SAS patients who did not agree to stop the use of agents or those who did not agree to receive continuous positive airway pressure (CPAP) or surgical treatment were also excluded.

All patients were asked to stop antihypertensive agents when admitted to hospital. Antihypertensive agents were stopped for 2 weeks in order to eliminate the influence of agents completely. After 3 days but within 1 week of admission, the plasma Ang II concentration was tested and ambulatory blood pressure (ABP) and polysomnography (PSG) monitoring were performed. The Ang II concentration, ABP, and PSG were reexamined 3 months after CPAP or surgical treatment. All patients signed informed consent form and the study protocol was approved. The study was approved by the Ethics Committee of our hospital.

A total of 204 patients were included in the trial. Of these patients, 15 cases were lost 3 months later when the reexamination of Ang II, ABP and PSG was done, while another 9 patients were excluded for incomplete data.

Thus, a total of 180 patients were included in this study, which included 104 males and 76 females. Patients' age ranged from 44 to 70 years old (average age: 52 ± 10 years old). Ninety-eight cases had smoking history. For 38 cases of diabetes mellitus, 33 cases took oral antidiabetic drug or received hypodermic injection of insulin to control their blood glucose levels, other 5 cases with diabetes controlled

their blood glucose with diet. For 46 cases of hyperlipidemia, 35 patients orally took lipid lowering drugs, and 32 of them had normal blood fat level. Eleven newly diagnosed hyperlipidemia patients, who did not agree for drug therapy, controlled their hyperlipidemia by dietary therapy. A total of 164 patients orally took aspirin. Aspirin therapy was discontinued for those in need of surgery 1 week prior to operation, and restarted if no hemorrhagic tendency was found within 4 weeks postoperatively.

PSG monitoring

At least 7-hour monitoring at night was performed by a POLYSMITH PSG analyzer and the following parameters were measured: electroencephalogram (EEG), eye movement, electromyogram (EMG), nasal and oral airflow, chest and abdominal wall motion, electrocardiogram, and blood oxygen saturation (SaO₂). SAS was diagnosed according to the following criteria made by American Academy of Sleep Medicine in 2009.⁹ (1) Apnea was defined as a complete cessation of nasal and oral airflow for more than 10 seconds. Obstructive sleep apnea was defined as the presence of chest/abdominal wall motion in the absence of nasal and oral airflow. (2) Hypoventilation was defined as a decrease in respiratory airflow intensity (amplitude) at least 50% during sleep combined with SaO₂ decreased by 4% or greater. (3) Obstructive SAS was defined as apnea or hypoventilation caused by repeated complete or partial upper airway obstruction in the presence of chest/abdominal wall motion. Central SAS was defined as cessation of nasal and oral airflow for more than 10 seconds and disappearance of abdominal wall motion. (4) Apnea-hypopnea index (AHI) was defined as the number of obstructive apneas and obstructive hypopneas per hour of sleep. The severity of SAS was classified as follows according to AHI: non-SAS (AHI<5), mild SAS (5≤AHI<20), moderate SAS (20≤AHI<40), and severe SAS (AHI≥40).

Determination of Ang II concentration using ELISA

A total of 5 mL of elbow venous blood was collected from every patient between 7:00 AM and 9:00 AM after they woke up and rested for 15 minutes in a supine position. Plasma Ang II concentration was analyzed by an ELISA (R&D Systems Inc., MN, USA).

Twenty-four hours ABP monitoring

A non-invasive ABP monitoring system (MOBEL-O-GRAPH, Industrial Equipment and Machinery Limited Company, Mainz, Germany) was used. The cuff was 22 cm×12 cm and wrapped around the left upper arm of the patient. The cuff

inflation was from 40 to 220 mm Hg and the deflation rate was 2 mm Hg/s. The system was set to obtain readings at 30-minute intervals from 6 AM to 10 PM and every 60 minutes from 10 PM to 6 AM. The blood pressure monitoring time was 24 hours and more than 30 measurements were done over the 24-hour period. Patients with nocturnal fall in blood pressure ≥10% or greater than 10 mm Hg were categorized as having dipper hypertension and those with nocturnal fall less than 10% or less than 10 mm Hg were categorized as non-dipper hypertension.

Treatment

CPAP was used for central SAS patients and those who did not agree to surgical treatment (*n*=72). Twenty-eight obstructive SAS patients underwent uvulopalatopharyngoplasty, hard palate shortening, and tongue body ablation. Eight obstructive SAS patients with glossoptosis received uvulopalatopharyngoplasty, hard palate shortening, tongue body ablation, and tongue base traction.

Statistical analysis

SPSS 10.0 was used for statistical processing and the data were expressed as $\bar{x} \pm s$. For quantitative data, a paired *t* test was performed to compare the intra-group differences and an analysis of variance was used for comparing the inter-group differences. *P* value less than 0.05 was considered as statistically significant and *P* value less than 0.01 was considered as highly significant.

RESULTS

Baseline indexes

According to the values of AHI, the patients were divided into an essential hypertension group (EH group, *n*=72), an essential hypertension with mild SAS group (EH+mild SAS group, *n*=60), and an essential hypertension with moderate and severe SAS group (EH+moderate-severe SAS group, *n*=48). No significant differences were found in patients' age, sex, body mass index, head circumference, neck circumference, baseline blood pressure, and incidence of diabetes as well as hyperlipemia among the different groups (all *P*>0.05). These results are shown in Table 1.

Comparison of sleep and respiratory parameters in each group

The average SaO₂ of the EH combined with SAS group before treatment was significantly lower than that of the EH group (all *P*<0.05). The patients in the EH combined with SAS group had a poor quality of sleep and more arousal

times compared with those with EH alone (all $P<0.05$). The lowest SaO_2 , average SaO_2 , and quality of sleep of EH patients combined with SAS were improved after CPAP or surgical treatment (all $P<0.05$, Table 2).

Concentration of plasma Ang II before and after treatment in each group

The concentration of plasma Ang II in the EH with mild SAS and EH with moderate-severe SAS before CPAP or surgical treatment was significantly higher than that in the EH group (all $P<0.05$). CPAP or surgical treatment significantly decreased the plasma Ang II level of EH patients combined with SAS (all $P<0.05$, Table 2).

ABP before and after treatment in each group

No significant difference was found in the resting blood pressure among the different groups ($P>0.05$). In the EH group, the incidence of non-dipper blood pressure curve was 31.9%, and those for hypertensive patients with mild SAS and moderate-severe SAS were 51.7% and 58.3%, respectively. The incidence of non-dipper blood pressure curve in the EH patients with mild SAS was significantly higher than that of patients with EH alone ($P<0.05$). The EH plus moderate-severe SAS group had the highest incidence of non-dipper blood pressure curve ($P<0.01$). After treatment, the incidence of non-dipper blood pressure curve in EH plus mild SAS and moderate-severe SAS groups was 38.3% and 39.6%, respectively. The incidence of non-dipper blood pressure significantly decreased after treatment within each group (all $P<0.05$, Table 3).

Table 1. General information in three groups[§]

Group	Case no.	Gender (Male/female)	Age (yr)	BMI (kg/m ²)	Head circumference (cm)	Neck circumference (cm)	Baseline BP (mm Hg)
EH	72	42/30	52±9	25.5±3.8	61.6±4.1	40.3±2.4	152±6/94±9
EH+mild SAS	60	34/26	51±10	26.3±4.2	62.2±3.6	42.5±3.0	160±5/92±8
EH+moderate-severe SAS	48	28/20	50±11	25.9±4.1 ^a	62.5±3.8	41.7±2.8	158±8/93±13
Group	Case no.	Case no. of smoking(%)	Case no. of diabetes(%)	Case no. of hyperlipemia(%)	Case no. of oral drug therapy		
					Aspirin (%)	Hypoglycemic agents* (%)	Statins* (%)
EH	40(55.6)	15(20.8)	18(25.0)	66(91.7)		13(86.7)	14(77.8)
EH+mild SAS	32(53.3)	13(21.7)	16(26.7)	54(90.0)		11(84.6)	12(75.0)
EH+moderate-severe SAS	26(54.2)	10(20.8)	12(25.0)	44(91.7)		9(90.0)	9(75.0)

§: Plus-minus values are means±SD.

EH: essential hypertension; SAS: sleep apnea syndrome; BMI: body mass index; BP: blood pressure.

*are expressed as the percentage of the number of patients with diabetes mellitus or hyperlipidemia in each group.

Table 2. Comparison of AHI, SaO_2 , and plasma Ang II values before and after treatment in each group[§]

Group		Case no.	AHI	SaO_2 (%)		Ang II (ng/mL)
				Lowest	Average	
EH		72	6±4	93.5±2.0	98.4±0.8	13.42±3.27
EH+mild SAS	Before treatment	60	16±4*	86.2±2.8*	91.5±6.0*	16.17±3.82*
	After treatment		8±6 [#]	90.3±2.6 [#]	94.8±8.0 [#]	14.67±2.56 [#]
EH+moderate-severe SAS	Before treatment	48	43±8*	77.9±8.0*	91.1±8.0*	18.73±4.05*
	After treatment		27±9 [#]	89.6±1.4 [#]	93.2±1.0 [#]	15.03±3.41 [#]

§: Plus-minus values are means±SD.

AHI: apnea-hypopnea index; SaO_2 : blood oxygen saturation; Ang II: angiotensin II.

* $P<0.05$ compared with EH group; [#] $P<0.05$ compared with same group before treatment.

Table 3. Comparison of ambulatory blood pressure and incidences of dipper- or non-dipper hypertension in each group[§]

Group		Case no.	24-hour BP (mm Hg)		Day-time BP (mm Hg)		Night-time BP (mm Hg)		Dipper hypertension		Non-dipper hypertension	
			SBP	DBP	SBP	DBP	SBP	DBP	No.	%	No.	%
EH		72	152±6	94±9	158±10	96±12	138±11	82±10	49	68.1	23	31.9
EH+mild SAS	Before treatment	60	160±5*	92±8	165±11*	98±15	148±13*	88±8*	29	48.3*	31	51.7*
	After treatment		144±11 [#]	90±12	148±10 [#]	94±10 [#]	139±14 [#]	86±11	37	61.7 [#]	23	38.3 [#]
EH+moderate-severe SAS	Before treatment	48	158±8*	93±13	165±10*	96±11	149±13*	90±11*	20	41.7*	28	58.3*
	After treatment		142±12 [#]	87±10 [#]	147±9 [#]	88±10 [#]	140±11 [#]	87±12 [#]	29	60.4 [#]	19	39.6 [#]

§: Plus-minus values are means±SD.

BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; day-time: 6 AM to 10 PM; night-time: 10 PM to 6 AM.

* $P<0.05$ compared with EH group; [#] $P<0.05$ compared with the same group before treatment.

DISCUSSION

SAS patients, regardless of whether they were combined with EH, had abnormal circadian rhythms of blood pressure during their sleep. The normal drop in blood pressure of SAS patients during sleep at night was terminated by frequent episodes of apnea. Nocturnal blood pressure, especially non-dipper blood pressure, was more important in predicting the mortality of cardiovascular complications compared with the day-time average blood pressure and 24-hour blood pressure in SAS patients.¹⁰ Even if the 24-hour ABP fluctuation was in the normal range of blood pressures (<130/80 mm Hg), the risk of cardiovascular death increased by 20% for each additional 5% increase of night- to day-time SBP or DBP ratio.¹¹

In this study we measured the plasma Ang II concentration and ABP of patients with essential hypertension alone or as well as SAS, to investigate the role of Ang II in blood pressure disorder of essential hypertension patients combined with SAS and find effective strategies to treat SAS. We found that the plasma Ang II concentration and incidence of non-dipper blood pressure in both EH+mild SAS and EH+moderate-severe SAS groups were significantly higher than those in the EH group, thereby suggesting that the loss of circadian rhythm of blood pressure was associated with Ang II, as well as SAS and its severity. Frequent arousals and apnea during sleep in SAS patients caused hypoxemia and change in chest wall pressure. Thus, the release of catecholamines and sympathetic nerve activity were increased, which caused acute changes in the heart, chest, body fluid and hemodynamics, as well as an increased Ang II. Subsequently, these pathological changes led to ventricular remodeling and changes in the circadian rhythm of blood pressure.¹² The above results indicated Ang II might be the vasoactive substance responsible for the alteration in the normal circadian pattern of blood pressure. After CPAP or surgical treatment, the plasma Ang II concentration and the proportion of non-dipper blood pressures of the two SAS groups were significantly decreased, thereby suggesting CPAP or surgical treatment could improve blood pressure disorder and decrease plasma Ang II level in patients with obstructive SAS. Early diagnosis and treatment of SAS in essential hypertensive patients could recover the circadian rhythm of blood pressure.

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