Compensatory Excretion of Prostacyclin and Thromboxane Metabolites in Obstructive Sleep Apnea Syndrome

Hiroshi Kimura, Mafumi Niijima, Yuzo Abe, Hidenori Edo, Hideo Sakabe, Akio Kojima, Kiyoshi Hasako, Shigeru Masuyama, Koichiro Tatsumi and Takayuki Kuriyama

Since obstructive sleep apnea syndrome (OSAS) is often linked with systemic hypertension, we sought to clarify the characteristics of prostanoid metabolism in OSAS. In 7 OSAS patients (apnea-hypopnea index, 51.0 ± 23.4) and 7 non-snorers as control, nocturnal urine was sampled and analyzed for stable metabolites of prostacyclin (PGI₂) and thromboxane A₂ (TXA₂), [6-keto-PGF₁α and thromboxane B₂ (TxB₂)]. The ratio of 6-keto-PGF₁α to TxB₂ was significantly higher in OSAS (2.97 ± 1.52) than in control (1.38 ± 0.38). Successful treatment with nasal continuous positive airway pressure (8.3 ± 1.5 cmH₂O) for 3 days caused a significant decrease in mean blood pressure in OSAS. Moreover, the 6-keto-PGF₁α to TxB₂ ratio also significantly decreased to 1.74 ± 0.58, a level which may not significantly different from control. These results suggest that the production ratio of PGI₂ to TXA₂ is shifted toward vasodilatation in untreated OSAS. We conclude that the production of prostanoids plays a role in compensating for the systemic hypertension in OSAS. (Internal Medicine 37: 127-133, 1998)

Key words: prostanoids, upper airway, continuous positive airway pressure, hypertension, arterial blood pressure

Introduction

It is well recognized that thromboxane A₂ (TXA₂) is a vasoconstrictor as well as a potent stimulus for platelet aggregation which can be antagonized by the vasodilator prostacyclin (PGI₂)(1-5). It is also suggested that there is a pathophysiological link between systemic hypertension and obstructive sleep apnea syndrome (OSAS) (6-8). However, the role of the metabolism of prostanoids in OSAS remains elusive. Christman et al have reported that there is an increase in the 24-hour excretion of TXA₂ as well as a decrease in that of prostacyclin in the primary as well as in the secondary form of pulmonary hypertension (3), suggesting that the imbalance in the release of these prostanoids is involved in the development and persistence of pulmonary hypertension.

Any stimulation of the arachidonate cascade such as via platelet activation potentially induces the increased vascular tone by TXA₂ in association with a decrease in the production of PGI₂, resulting in pathologic stimulation coinciding with hypertension (9, 10). Furthermore, OSAS is accompanied by pulmonary hypertension and systemic hypertension in 10–20% (7, 11, 12) and 50–60% of all the cases (6–8, 13), respectively.

Accordingly, it may be of major importance to investigate the role of the arachidonate cascade pathway and its enzymes as they are essentially involved in the maintenance of balance in the smooth muscle tone of the respiratory tract and in pulmonary vasculature.

In the present study we investigated 1) whether the characteristics in the production of PGI₂ and TXA₂ during sleep are different in OSAS compared to control, and 2) how nasal continuous positive airway pressure (CPAP) influences prostanoid production and systemic blood pressure in OSAS.

Subjects and Methods

Subjects

Seven patients with OSAS and 7 non-obese and non-snorer subjects as control subjects were investigated in the present study. Informed consent was obtained from all subjects. All of them were non-smokers and not taking nonsteroidal anti-inflammatory or anti-hypertensive drugs. Mean age and body mass index (BMI) were 44 ± 12 (SD) years and 28.7 ± 4.3 kg/m² in OSAS, and 34 ± 4 years and 23.9 ± 6.4 kg/m² in the control, respectively. In control, mean age and BMI were not

From the Department of Chest Medicine, Chiba University School of Medicine, Chiba
Received for publication August 18, 1997; Accepted for publication December 27, 1997
Reprint requests should be addressed to Dr. Hiroshi Kimura, the Department of Chest Medicine, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-0856
Kimura et al

significantly different from OSAS (Table 1). All patients exhibited a moderate to severe degree of apnea-hypopnea index (AHI) from 21 to 86, and the mean AHI was 51.0 ± 23.4. The ratios of oxygen desaturation time exhibiting arterial oxygen saturation (SaO₂) less than 90% and 80% to total sleep time were 54.0 ± 35.5 and 29.3 ± 30.9%, respectively (Table 1). None of the OSAS patients was hypoxic during wakefulness, and 2 of them were hypercapnic with partial pressure of carbon dioxide (PaCO₂) of more than 45 mmHg. Systemic hypertension measured in the early morning, defined as systolic blood pressure higher than 160 mmHg or diastolic blood pressure higher than 95 mmHg, was observed in 4 of 7 OSAS patients. On the contrary, none of the control showed hypertension. Therefore, the mean arterial blood pressure was significantly higher in OSAS than in control (Table 1).

Sleep study protocol

In patients with OSAS, nocturnal urine was sampled according to the manner described below. Blood pressure was measured with 24-hour monitoring by automated ambulatory blood pressure monitor (ABPM) including the first night. During the second night, sleep study was performed without nasal CPAP. For the third night, an appropriate level of nasal CPAP (CPAP Model 7100, Healthdyne Technologies, Marietta, GA, USA) was determined during the sleep study so as to maintain lowest SaO₂ at more than 90% during non-rapid eye movement (NREM) and at 85% during rapid eye movement (REM) sleep, and these levels were also kept during the fourth night. At the fifth night, i.e., the third night after starting the application of nasal CPAP, urinary sampling was again performed simultaneously with the monitoring of 24-hour arterial blood pressure.

Urinary sampling and analysis

OSAS patients were asked to fully micturate at midnight and after that urine samples were collected during the period until 6 am if provided, and again taken at 6 am from all patients (6 hour after total micturition). Urine volume for 6-hour, and urinary concentrations of the stable metabolites of PGI₂ and TxA₂, [6-keto-PGF₁α and thromboxane B₂ (TxB₂)] were measured by high performance liquid chromatography (HPLC) and specific immunoassays (14, 15). Urinary sampling in control was done by the same schedule as OSAS, with the measurement of arterial blood pressure in the early morning.

Statistical analyses

All values were expressed as mean ± 1SD. The effect of nasal CPAP was compared between before and 3 days after its start by Wilcoxon test or Student’s t-test for paired values. For evaluating the relationship between various parameters obtained during sleep and the excretion of prostanoids, the least squares regression method was used. P values less than 0.05 were considered statistically significant.

Results

Effects of nasal CPAP during sleep on sleep parameters and blood pressure

The effects of nasal CPAP on AHI, on O₂ desaturation, as well as mean arterial blood pressure taken at 6 am in a supine position were compared before and 3 days after its start (Fig. 1).

Table 1. Profiles of OSAS and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>OSAS</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>(M:F)</td>
<td>7:0</td>
<td>7:0</td>
</tr>
<tr>
<td>Age</td>
<td>(yr)</td>
<td>44 ±12</td>
<td>34 ± 4</td>
</tr>
<tr>
<td>Height</td>
<td>(cm)</td>
<td>165.1 ±7.0</td>
<td>172.0 ±3.6</td>
</tr>
<tr>
<td>Body weight</td>
<td>(kg)</td>
<td>78.7 ±15.8</td>
<td>70.2 ±12.2</td>
</tr>
<tr>
<td>BMI</td>
<td>(kg/m²)</td>
<td>28.7 ±4.3</td>
<td>23.8 ±4.6</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td>7.38 ±0.02</td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>(mmHg)</td>
<td>43.2 ±3.2</td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>(mmHg)</td>
<td>82.2 ±10.9</td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td></td>
<td>51.0 ±23.4</td>
<td></td>
</tr>
<tr>
<td>SaO₂ ≤90%/TST (%)</td>
<td></td>
<td>54.0 ±35.5</td>
<td></td>
</tr>
<tr>
<td>SaO₂ ≤80%/TST (%)</td>
<td></td>
<td>29.3 ±30.9</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>(mmHg)</td>
<td>141.4 ±15.0</td>
<td>122.3 ±8.6</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>(mmHg)</td>
<td>89.7 ±16.7</td>
<td>73.1 ±4.5</td>
</tr>
<tr>
<td>Mean BP</td>
<td>(mmHg)</td>
<td>107.0 ±15.2</td>
<td>89.5 ±5.6</td>
</tr>
</tbody>
</table>

BMI: body mass index, SaO₂ ≤90%/TST: ratio of oxygen desaturation time exhibiting SaO₂ of less than 90% to total sleep time, SaO₂ ≤80%/TST: ratio of oxygen desaturation time exhibiting SaO₂ of less than 80% to total sleep time, systolic BP: systolic arterial blood pressure, diastolic BP: diastolic arterial blood pressure, mean BP: mean arterial blood pressure, NS: not significant between OSAS and control. (mean ± SD)
AHI decreased from 51.0 ± 23.4 to 5.9 ± 5.9 (p < 0.01), and sleep oxygen desaturation time, less than 90% SaO₂, declined from 54.0 ± 35.5 to 2.4 ± 3.7% (p < 0.01) by the application of an appropriate level of nasal CPAP (8.3 ± 1.5 cmH₂O). The decrease in arterial blood pressure manually measured in the early morning was greater in patients with hypertension than in those without; the magnitude of decrease in mean blood pressure with and without hypertension was 10.2 ± 7.7 and 4.7 ± 0.7, respectively. Diastolic and mean blood pressure averaged for both groups decreased from 89.7 ± 16.7 to 83.0 ± 11.9 (p < 0.05), and 107.0 ± 15.2 to 100.7 ± 12.4 mmHg (p < 0.05), respectively. On the other hand, systolic blood pressure changed from 141.4 ± 15.0 to 136.0 ± 17.4 mmHg, without a significant difference (p = 0.066).

Effects of nasal CPAP on 24-hour blood pressure monitoring

For the purpose of evaluating the effect of nasal CPAP on the time course of 24-hour blood pressure, the mean arterial pressure level was plotted in terms of the differences from the mean values obtained just 1 hour before starting sleep (Fig. 2). Without nasal CPAP, the daily profile of arterial blood pressure exhibited little change throughout a 24-hour period, i.e., a non-dipper pattern was observed in OSAS without nasal CPAP treatment. On the other hand, successive 3-night treatment by CPAP caused a dipper pattern tendency, i.e., blood pressure showed decreasing trends during the night, although not to a statistically significant degree.

Effects of nasal CPAP on the excretion rate of prostanoids

Nasal CPAP produced a significant decrease in urine volume for 6 hour from 284 ± 119 to 210 ± 72 ml (p < 0.05). Urinary concentrations of 6-keto-PGF₁α and TxB₂ were not significantly changed by nasal CPAP, from 0.363 ± 0.152 to 0.281 ± 0.100 and from 0.134 ± 0.064 to 0.179 ± 0.079 ng/ml, respectively. Eventually, the excretion rate of 6-keto-PGF₁α per minute decreased at a borderline significance (p = 0.053) to a 60% level of the pre-CPAP value, from 283 ± 173 to 171 ± 106 pg/min by nasal CPAP. On the other hand, TxB₂ excretion remained at almost the same level, 101 ± 61 without nasal CPAP and 113 ± 79 pg/min with CPAP.

The balance in the excretion of urinary prostanoids, that is, the excretion ratio of 6-keto-PGF₁α to TxB₂, was evaluated (Fig. 3). The ratio of 6-keto-PGF₁α to TxB₂ in the urinary sample for 6 hour was significantly higher in the untreated OSAS patients (2.97 ± 1.52) than in the control (1.38 ± 0.38; p < 0.05). Moreover, the ratio significantly decreased with nasal CPAP treatment to 1.74 ± 0.58 (p < 0.05; compared to no treatment), a level not significantly different from control.

Correlation between CPAP-induced changes in sleep parameters and prostanoid excretion

The relationships between CPAP-induced changes in the excretion of prostanoids and those of nocturnal parameters...
Figure 2. Daily profiles of mean arterial blood pressure before nasal CPAP and 3 days after starting treatment. Mean arterial pressure level was plotted in terms of the differences from the mean values obtained just 1 hour before starting sleep (Δmean BP: Δmean arterial blood pressure) in 6 OSAS patients. A non-dipper pattern observed without nasal CPAP was changed to a dipper pattern by CPAP treatment. ●: off CPAP, before nasal CPAP treatment, ○: on CPAP, 3 days after starting nasal CPAP. Each bar represents mean ± SD.

Figure 3. Urinary excretion ratios of 6-keto-PGF₁₀ to TxB₂ before nasal CPAP treatment and 3 days after starting nasal CPAP in OSAS and in the control. The ratio was significantly higher in the untreated OSAS patients than in control, and it decreased significantly by nasal CPAP. 6kPGF₁₀/TxB₂: the ratio of 6-keto-PGF₁₀ to thromboxane B₂, off CPAP: before nasal CPAP treatment, on CPAP: 3 days after starting nasal CPAP. Each bar represents mean ± SD.
were plotted in Fig. 4. The magnitudes of the improvement of AHI and O₂ desaturation, and those of the decrease in mean blood pressure in the early morning were plotted against the percent changes in the 6-keto-PGF₁α to TxB₂ ratios by the application of nasal CPAP. A relatively high correlation was observed between the decrease in mean blood pressure and % 6-keto-PGF₁α/TxB₂ (r=0.62). % 6kPGF₁α/TxB₂, the percent change in the ratio of 6-keto-PGF₁α to thromboxane B₂ by the application of nasal CPAP. ∆mBP: the magnitude of the decrease in mean blood pressure in the early morning before and after nasal CPAP.

Discussion

The present study demonstrates that the urinary excretion ratio of 6-keto-PGF₁α to TxB₂ during sleep was significantly higher in untreated OSAS than in control subjects. Nevertheless, arterial blood pressure was higher in OSAS than control. Furthermore, the successful application of nasal CPAP significantly decreased this ratio in association with a tendency to lower arterial blood pressure. These results might imply that the overall function of the prostanoid metabolism play a role in producing vasodilation in untreated OSAS, i.e., the increased production of 6-keto-PGF₁α to TxB₂ is not the cause of the raised blood pressure, but rather the result of it. So, it might be considered that the increase in the 6-keto-PGF₁α to TxB₂ ratio indicates a kind of compensatory reaction, suggesting that either the production of PGI₂ is more upregulated in OSAS than control, or that of TxB₂ is more downregulated. Nasal CPAP caused a significant decrease in diastolic blood pressure but a less than significant decrease in systolic blood pressure, suggesting that nasal CPAP more effectively influenced peripheral vascular tone rather than the overall cardiac function in the present study. It is conceivable that the compensatory reaction of prostanoids observed caused sufficient vasodilative action in the untreated condition, but this level may not have been the absolute maximum because CPAP seemed to produce further vasodilatation. In the present study, the changes in excretion levels of PGI₂ and TxA₂ as calculated per minute did not reach significant differences. It is likely that the ratio represents a reliable index for evaluating the prostanoid balance independent of the urinary volume.

Christman et al have shown an increase in the 24-hour excretion of TxA₂ as well as a decrease in that of prostacyclin in both primary and secondary pulmonary hypertension (3). This suggests that the imbalance in prostanoids is involved in the development and persistence of pulmonary hypertension. It is assumed that endothelial damage which is inevitably accompanied by remodeling or organic change causes a deterioration of PGI₂ production in patients with pulmonary hypertension, as the vascular beds in pulmonary arteries and/or arterioles are considered to be the main sites producing PGI₂ (1-5). However, it has not been clearly determined whether pulmonary vascular beds responsible for the production of PGI₂ are functionally preserved or not in OSAS. Sheer stress in pulmonary vascular beds can be observed in various kinds of physiological and pathological situations such as hypoxic pulmonary vasconstriction (HPV) and increased cardiac output. Hypoxia is generally known to be a cause of pulmonary as well as systemic hypertension (16). An ineffective respiratory effort which causes a dramatic increase in the fluctuations of intrathoracic pressure during obstructive apnea also functions as a stimulus for PGI₂ production in pulmonary vascular beds. These characteristic changes are especially recognized in association with negative pressure elicited during inspiratory efforts (17). Moreover, increase in cardiac output is also accompanied by accentuated intrathoracic pressure, both of which can influence pulmonary vessels via sheer stress. Increased sympathetic activity in asso-
blood pressure regulation in spontaneously hypertensive rats. Where increased production of TxA2 takes part in the systemic blood pressure have also been reported in animal experiments, of PGI2 in several vascular models (28). The effects of TxA2 on TxA2 to PGI2 ratio (28), and that it diminished the production that the chronic administration of cyclosporine-A increased the rate of thromboembolic complications (27). It was also reported with the occurrence of systemic hypertension and an increasing rate (26). However, cyclosporine-A is known to be associated important in the prevention of rejection in the field of transplantation (29).

Among immunosuppressant agents, cyclosporine-A is important in the prevention of rejection in the field of transplantation (26). However, cyclosporine-A is known to be associated with the occurrence of systemic hypertension and an increasing rate of thromboembolic complications (27). It was also reported that the chronic administration of cyclosporine-A increased the TxA2 to PGI2 ratio (28), and that it diminished the production of PGI2 in several vascular models (28). The effects of TxA2 on blood pressure have also been reported in animal experiments, where increased production of TxA2 takes part in the systemic blood pressure regulation in spontaneously hypertensive rats (9) and Lyon strain rats (10), which also suggests that the ratio of PGI2 to TxA2 can be considered as an index of vasodilating activities from the viewpoint of prostanoid metabolism.

Prostanoids are cyclooxygenase metabolites of arachidonic acid and are considered to be one of the regulatory factors maintaining homeostasis that is closely related to endothelial function (29). It has been elucidated that the functional roles of the endothelium mainly include (a) activation and inhibition of circulating and local vasoactive hormones, (b) producing substances involved in coagulation, and (c) synthesizing and releasing vasoactive substances; PGI2 and nitric oxide act as vasodilators and platelet function inhibitors whereas TxA2 and endothelin are vasoconstrictor substances. Endothelium-derived relaxing substances predominantly appear to function under physiological conditions (30). In contrast, in the hypertensive and atherosclerotic arteries, the release of relaxing substances or the responsiveness of vascular smooth muscle cells to them is reduced while the release of endothelium-derived constricting factors is augmented, suggesting that the imbalance between relaxing and constricting substances plays a role, at least in part, in the pathogenesis of hypertension (29, 30).

It has been reported that impaired vascular PGI2 generation and enhanced TxA2 production occur in Dahl genetic strain rats susceptible to salt-induced hypertension (Dahl S) with borderline line hypertension (31). However, both vascular PGI2 and vascular PGI2 synthase activity are increased in accordance with blood pressure elevation in this model, which contribute to the restoration of vascular capacity to generate PGI2, suggesting that high blood pressure is a potential activator of vascular PGI2 synthase. Moreover, since PGI2 synthase activity is unaltered in Dahl S rats with borderline hypertension, the impaired PGI2 generation might be due to a decrease in arachidonate liberation or a lowered conversion of arachidonate to PGH2 (32). These findings seem to imply that the enhanced PGI2 generation and the increased PGI2 synthase are beneficial in treating high blood pressure and in protecting against the subsequent vascular wall damage in this animal model. Taking the evidence mentioned above into account, in the present study, it is likely that the relatively enhanced PGI2 production observed in OSAS also represents the beneficial effects on blood pressure regulation.

It seems important that nasal CPAP produced at least a tendency of a negative correlation between the degree of change in the ratio of PGI2 to TxA2 and the magnitude of decrease in blood pressure. This implies that the more the blood pressure is lowered, the more the PGI2 to TxA2 ratio will be decreased in OSAS patients. More patients will have to be investigated to confirm these results, because the effect of lowering blood pressure must depend on the untreated level of baseline blood pressure.

From the present study, we are led to believe that the production ratio of prostacyclin to thromboxane might be one of the key determinants in the susceptibility for nocturnal hypertension in patients with OSAS. Moreover, it is likely that there is some relationship between the effectiveness of nasal CPAP on the decrease in production of the elevated prostacyclin.
to TxB2 ratio and the decrease in mean blood pressure. These correlations lend support to the hypothesis that patients who develop hypertension are those in whom the protective mechanism of prostacyclin release has failed. Furthermore, a valid interpretation might be that some OSAS patients excessively produce PGI2 in response to elevated blood pressure during the night because an excess amount of PGI2 is no longer needed once the elevated blood pressure is improved by CPAP treatment. However, we cannot sufficiently explain why the present data differed from that of Krieger et al (21). To clarify these issues, further studies with greater numbers of subjects will need to be performed, although collecting a sufficient number of OSAS patients who had been free of nonsteroidal anti-inflammatory and anti-hypertensive drugs may pose a problem.

In conclusion, the present data suggest that the relative levels of PGI2 to TxA2 were shifted toward vasodilatation in untreated OSAS. Therefore, it is concluded that the production of prostanooids plays a part in compensating for systemic hypertension in OSAS. This result is essentially different from that in the primary and secondary forms of pulmonary hypertension.

Acknowledgements: The authors thank Dr. Yoshiyuki Honda for reading the manuscript and for his helpful advice. Portions of this work have been presented at the Mini-Symposium of the 1994 International Conference of American Thoracic Society and appeared in abstract form in Am. J. Respir. Crit. Care Med., 149, A809, 1994. H. Kimura received the III Pneumo Forum Prize for part of this work in 1994. This study was supported in part by a grant from the Research Committee, Intractable Respiratory Failure, the Ministry of Health and Welfare of Japan.

References