Changes in Urinary Uric Acid Excretion in Obstructive Sleep Apnea Before and After Therapy With Nasal Continuous Positive Airway Pressure*

Hamid Sahebjami, MD, FCCP

**Study objective:** To assess the utility of urinary uric acid excretion as a marker of nocturnal hypoxia in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) before and after the institution of nasal continuous positive airway pressure (CPAP).

**Design:** Prospective, open.

**Setting:** Sleep Disorders Laboratory, Veterans Affairs Medical Center.

**Participants:** Thirty consecutive male subjects, 20 with OSAHS and 10 without OSAHS.

**Measurements and methods:** Spot morning urine and venous blood samples were obtained in all subjects; samples were also obtained after the application of CPAP in those with OSAHS. Uric acid excretion, normalized to creatinine clearance, was calculated as the product of urinary uric acid and serum creatinine concentrations divided by urine creatinine concentration. In patients with OSAHS, uric acid excretion was 0.55±0.1 mg/dL before CPAP therapy and decreased to 0.30±0.01 mg/dL after CPAP therapy (p<0.001). The latter value did not differ significantly from the mean value (0.32±0.03 mg/dL) in the control group. Uric acid excretion in OSAHS patients correlated significantly with the apnea-hypopnea index (r=0.42; p<0.0003).

**Conclusion:** Uric acid excretion is increased in OSAHS patients and normalizes after CPAP treatment, most likely reflecting differences in tissue oxygenation between the two conditions. Further studies in large number of patients may confirm the usefulness of this simple test for diagnosis and follow-up of patients with OSAHS. (CHEST 1998; 113:1604-08)

**Key words:** anaerobic metabolism; sleep disorders; uric acid excretion

**Abbreviations:** ADP=adenosine diphosphate; AMP=adenosine monophosphate; ATP=adenosine triphosphate; CI=confidence interval; CPAP=continuous positive airway pressure; OSAHS=obstructive sleep apnea-hypopnea syndrome; SaO2=arterial saturation of oxygen

The integrity of cellular metabolic processes depends on the adequate supply of oxygen—oxygen delivery—for the preservation and maintenance of aerobic metabolism. Oxygen consumption by tissues represents the aerobic production of adenosine triphosphate (ATP), a crucial compound for maintaining cellular homeostasis. Under hypoxic conditions, when oxygen supplies are inadequate to meet oxygen demands of the cells, formation of ATP from adenosine diphosphate (ADP) is impaired and a net degradation of ATP to ADP and adenosine monophosphate (AMP) occurs. This leads to the release of purine nucleotide intermediates (adenosine, inosine, hypoxanthine, and xanthine) and the purine catabolic end product, uric acid. Elevated levels of ATP degradation products in bodily fluids, therefore, represent a marker for cell energy crisis as a result of cellular hypoxia. Increased levels of ATP degradation products, as a marker of ischemia and hypoxia, have been reported in isolated organs of animals and in human studies. Furthermore, clinical studies have shown increased amounts of these products in neonates with infant respiratory distress syndrome, during strenuous exercise, in patients with hypotension or acute respiratory failure, and in critically ill patients.

Three studies have examined the utility of an overnight change in urinary uric acid:creatinine ratio as a marker of tissue hypoxia in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) compared with control subjects. Results of these studies have been conflicting and have revealed that

*From the Pulmonary and Critical Care Section, Veterans Affairs Medical Center, and the Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio. Manuscript received July 22, 1997; revision accepted November 5, 1997.

Reprint requests: Hamid Sahebjami, MD, FCCP, VA Medical Center, 3200 Vine St, Cincinnati, OH 45220.
the overnight change in the urinary uric acid:creatinine ratio has poor sensitivity in detecting nocturnal hypoxemia and does not correlate with disordered breathing events or associated desaturation. Furthermore, two sets of blood and urine samples—both evening and morning—are necessary for the calculation of this ratio.

A simple, convenient method for assessing urinary uric acid excretion has been described and validated in normal adult men and gouty patients. According to this method, uric acid excretion is measured in milligrams of urinary uric acid per deciliter of glomerular filtrate using spot urine and venous blood samples. In addition to its simplicity, this test is more physiologic than the urinary uric acid:creatinine ratio because uric acid excretion is normalized to creatinine clearance.

The goal of the present preliminary study was to assess the utility of urinary uric acid excretion as a marker of hypoxia in patients with OSAHS before and after the institution of therapy with nasal continuous positive airway pressure (CPAP) and to compare it with the utility of the urinary uric acid:creatinine ratio obtained under similar conditions.

**Materials and Methods**

**Patients**

Thirty male subjects referred to the Sleep Disorders Laboratory at the Cincinnati Veterans Affairs Medical Center for polysomnography were studied. Twenty men were found to have OSAHS; the remaining 10 had no evidence of disordered breathing and served as controls.

**Measurements**

Flow rates, lung volumes, and single-breath carbon monoxide diffusing capacity were determined using an automated system (Collins model GS/Plus; Warren E. Collins Inc; Braintree, Mass). Recommendations for standardized procedure for lung function testing were followed. Predicted equations for pulmonary function tests were from Knudson et al, Goldman and Becklake, and Gaensler and Smith.

Arterial blood samples were drawn from the radial artery with the patient in a sitting position while breathing room air. Arterial blood gas analysis was performed using the ABG-520 system (Radiometer American Inc; Westlake, Ohio).

Details of technique and scoring polysomnography in our sleep laboratory have been published previously. For staging sleep, EEGs (two channels), chin electromyogram (one channel), and electro-oculograms (two channels) were recorded. Thoracobdominal excursions and airflow were measured qualitatively. Arterial oxyhemoglobin saturation was recorded using an ear oximeter (Biox IIA; BT, Inc; Boulder, Colo). These variables were recorded on a multichannel polygraph (Model 78D; Grass Instrument; Quincy, Mass). Apnea was defined by the cessation of inspiratory airflow for at least 10 s in the presence of thoracic and abdominal excursions. A hypopnea was defined by a reduction of airflow for at least 10 s that was associated with at least a 4% reduction in overnight oxyhemoglobin desaturation or arousals. The time spent below saturation of 88% was measured manually.

A urine specimen and a venous blood sample were collected in the morning after the completion of polysomnography. To some of the urine specimens, 5% sodium hydroxide was added and pH was adjusted to greater than 8. The urine was stored at 4°C. Urinary uric acid concentration was measured enzymatically according to the method described by Tietz. Sodium, creatinine, and uric acid concentrations were measured in the blood specimen and the remaining urine specimen, using standard techniques. Uric acid excretion was calculated as the product of urine uric acid and serum creatinine concentrations divided by urine creatinine concentration, all in mg/dL.

Patients were told to avoid drinking caffeinated beverages during the hospital stay as a routine instruction for conducting sleep studies. They continued taking medications as prescribed by their physicians. Urine passed during polysomnography was discarded. After the diagnosis of OSAHS was established during the first night of study, patients underwent a second night of polysomnography with the application of adequate levels of CPAP to eliminate apnea-hypopnea and maintain an arterial oxyhemoglobin saturation above 90%.

**Statistical Analysis**

For each parameter measured or calculated, values for the individual patients in each group were averaged, and the SEM was calculated. Because the common variance assumption required by the t test was not appropriate for some of the measurements, the Kruskal-Wallis nonparametric analysis of variance test was used to assess the significance of differences among the three studies. A p value of less than 0.05 was considered significant with the significance adjusted by the Bonferroni-Dunn method. We calculated 95% confidence intervals (CIs) using the approximate degrees of freedom for the t statistics. Kendall’s nonparametric rank correlation coefficient of various parameters of uric acid excretion, as the dependent variable, was computed.

**Results**

Patients and the control group did not differ significantly in age and in body mass index (Table 1). Among pulmonary function tests and arterial blood gases, only total lung capacity was significantly different in the two groups (Table 1).

Polysomnographic parameters (Table 2) showed that in patients with OSAHS the apnea-hypopnea index was 53±6 episodes per h (CI, 39.2 to 66.9 episodes per h), which was associated with severe arterial oxyhemoglobin desaturation. During the second study night with CPAP, all polysomnographic parameters improved significantly in patients with OSAHS and were similar to those in the control group (Table 2).

Results of blood and urine tests are shown in Table 3. In patients with OSAHS, fractional excretion of sodium and uric acid excretion were significantly higher after the first night of study compared with the values obtained after the second night with CPAP and compared with the control group's values.
Mean uric acid excretion was 0.32±0.03 mg/dL (CI, 0.24 to 0.40 mg/dL) in the control group, 0.55±0.1 mg/dL (CI, 0.27 to 0.82 mg/dL) in patients before CPAP, and 0.30±0.01 mg/dL (CI, 0.26 to 0.34 mg/dL) in patients after CPAP therapy. Figure 1 shows individual values for uric acid excretion in patients and in the control group. One patient had a very high value before CPAP therapy, resulting in a large variation in this group; the inclusion or exclusion of this patient did not alter the statistical profile of the results. A significant correlation existed for all patients between uric acid excretion as the dependent variable and the apnea-hypopnea index (r=0.42; p<0.0003) and percent total sleep time with saturation less than 88% (r=0.32; p<0.01). The urinary uric acid:creatinine ratio was 27.2±2.8% (CI, 20.8 to 33.6%) in the control group, 50.1±13% (CI, 21.3 to 78.9%) in patients before CPAP, and 26.9±2.3% (CI, 22.3 to 31.5%) in patients after CPAP therapy. The urinary uric acid:creatinine ratio, as the dependent variable, correlated significantly with apnea-hypopnea index (r=0.34; p<0.003) and percent total sleep time with saturation less than 88% (r=0.28; p<0.02).

**DISCUSSION**

The results of this study revealed that in patients with OSAHS uric acid excretion was significantly higher before an overnight application of CPAP than after CPAP. Although there was a considerable overlap of individual values of uric acid excretion in control subjects and in OSAHS patients before CPAP therapy, in all but one subject the uric acid excretion fell following the institution of CPAP (Fig 1). Since the major difference between the two nights of study was the correction of hypoxemia by CPAP, it can be concluded that the change in uric acid excretion was most likely the result of differences in oxygenation during the two nights. However, numerous hormonal and sympathetic nervous system changes occur during the night in untreated OSAHS patients, which might have influenced urinary uric acid excretion independent of and in addition to tissue hypoxia.24-27

Three published reports have examined overnight changes in the uric acid:creatinine ratio in OSAHS. In two of these, a significant increase in the uric acid:creatinine ratio was observed in association with nocturnal hypoxemia; CPAP treatment led to a significant reduction in this ratio.13,14 The other study failed to confirm this observation.15 Collectively, these studies showed a substantial overlap and high variability of urinary uric acid:creatinine ratios among patients with OSAHS. This was reflected in a substantial number of false-negative findings of overnight change in this ratio and in the absence of any significant correlation between this ratio and various parameters of desaturation.

Thus, we chose to test the utility of urinary uric acid excretion, normalized to creatinine clearance, in patients with OSAHS before and after CPAP therapy. This is a more physiologic expression than the urinary uric acid:creatinine ratio because it corrects for the functional renal mass of the individual.16 Furthermore, it obviates the need for an additional evening collection necessary for the calculation of overnight change in urinary uric acid:creatinine ra-

### Table 1—Age, Body Mass Index, Pulmonary Function Tests, and Arterial Blood Gas Cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=10)</th>
<th>Patients (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57.7±3.3</td>
<td>55.1±2.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>33.9±2.9</td>
<td>30.6±1.9</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>84.8±5.0</td>
<td>77.1±3.1</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>78.1±6.5</td>
<td>75.2±3.5</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>73.9±3.5</td>
<td>78.6±1.5</td>
</tr>
<tr>
<td>Total lung capacity, %</td>
<td>96.8±2.8</td>
<td>85.7±3.2</td>
</tr>
<tr>
<td>Residual volume, %</td>
<td>111.0±9.0</td>
<td>100.8±8.5</td>
</tr>
<tr>
<td>Residual volume/total lung</td>
<td>109.6±7.7</td>
<td>109.1±5.5</td>
</tr>
</tbody>
</table>

Diffusion of carbon monoxide, % predicted 87.9±8.7 88.4±5.7
PaO₂, mm Hg 78.7±1.9 72.4±2.0
PaCO₂, mm Hg 39.1±0.5 42.5±1.1
pH 7.41±0.005 7.41±0.006

*Values are means±SEM.
*1p<0.05.

### Table 2—Polysomnography Data in Controls and in Patients With OSAHS Before and After Treatment With Nasal CPAP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=10)</th>
<th>Before CPAP</th>
<th>After CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dark time, min</td>
<td>386±3</td>
<td>380±3</td>
<td>390±6</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>311±15</td>
<td>295±10</td>
<td>329±11</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>83±3</td>
<td>76±2</td>
<td>82±3</td>
</tr>
<tr>
<td>Baseline SaO₂ %</td>
<td>95±0.5</td>
<td>93±0.4</td>
<td>93±3.4</td>
</tr>
<tr>
<td>Lowest SaO₂ during REM sleep, %</td>
<td>91±0.5</td>
<td>65±4</td>
<td>90±0.3</td>
</tr>
<tr>
<td>Lowest SaO₂ during non-REM sleep, %</td>
<td>90±0.6</td>
<td>66±5</td>
<td>90±0.2</td>
</tr>
<tr>
<td>Apnea-hypopnea index, episodes/h</td>
<td>5±3</td>
<td>53±6</td>
<td>1±0.6</td>
</tr>
<tr>
<td>SaO₂&lt;88%, min</td>
<td>0</td>
<td>10±8±24</td>
<td>4±1</td>
</tr>
<tr>
<td>SaO₂&lt;88%, % total sleep time</td>
<td>0</td>
<td>38±8</td>
<td>1±1</td>
</tr>
</tbody>
</table>

*Data presented as mean±SEM.
1SaO₂=arterial saturation of oxygen.
1p<0.001 vs other groups.
It is more convenient, less costly, and more physiologic, and therefore may prove to be more useful. In 19 of our 20 patients (95%), uric acid excretion was higher before the application of CPAP than it was after CPAP. False-negative results were found in only 1 of 20 patients (5%) with OSAHS, compared with previous reports of 17% and 30% false negativity. Importantly, the mean value of uric acid excretion in our study was similar in the control group (0.32±0.03 mg/dL) and in patients (0.30±0.01 mg/dL) after CPAP therapy (Table 3), suggesting that CPAP normalized uric acid excretion. We also compared changes in the urinary uric acid:creatinine ratio in the control group and in patients before and after CPAP therapy. This ratio was significantly higher before than after the institution of CPAP therapy (Table 3), confirming the results of previous studies.13,14

If the increase in uric acid excretion is a marker for cellular hypoxia, arterial oxyhemoglobin desaturation alone may not reflect its magnitude because arterial oxyhemoglobin saturation represents only one component of the oxygen delivery system. Of the other two major components, cardiac output and hemoglobin concentration, the latter was similar during the two study nights; the status of cardiac output during the two nights of study, however, could have been variable. Episodes of apnea-hypopnea and resultant hypoxemia and hypercapnia during the first study night, as well as application of CPAP during the second study night, could influence cardiac output leading to variable changes in oxygen delivery.28-30 It is interesting that in the present study, uric acid excretion best correlated with the apnea-hypopnea index (r=0.42; p<0.0003) rather than desaturation (r=0.32; p<0.01).

The results of this study also confirm increased nocturnal natriuresis in OSAHS patients and its normalization after CPAP therapy (Table 3).31 Natriuresis in these patients is in part due to a nocturnal increase in plasma levels of atrial natriuretic factors, which decrease after treatment with CPAP.31,32 Increased negative intrathoracic pressure and pulmonary vasoconstriction during sleep, with a resultant increase in right atrial pressure, are likely causes of enhanced secretion of atrial natriuretic factor in OSAHS.33,34

### Table 3—Blood and Urine Tests in Controls and in Patients With OSAHS Before and After Treatment With Nasal CPAP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=10)</th>
<th>Patients (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.2±0.6</td>
<td>1.2±0.07</td>
</tr>
<tr>
<td>Serum sodium, mg/dL</td>
<td>140.0±1.3</td>
<td>140.2±0.7</td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>7.2±0.6</td>
<td>6.6±0.2</td>
</tr>
<tr>
<td>Urinary creatinine, mg/dL</td>
<td>145.2±18</td>
<td>101.7±13</td>
</tr>
<tr>
<td>Urinary sodium, mg/dL</td>
<td>95.7±18</td>
<td>125.3±10</td>
</tr>
<tr>
<td>Urinary uric acid, mg/dL</td>
<td>40.4±7</td>
<td>38.7±5</td>
</tr>
<tr>
<td>Fractional excretion of sodium, %</td>
<td>0.53±0.09</td>
<td>1.4±0.11</td>
</tr>
<tr>
<td>Uric acid excretion, mg/dL</td>
<td>0.32±0.03</td>
<td>0.55±0.13</td>
</tr>
<tr>
<td>Urinary uric acid:creatinine, %</td>
<td>27.2±2.8</td>
<td>50.1±13.71</td>
</tr>
</tbody>
</table>

*Data presented as mean±SEM.

1p<0.01 vs control and p<0.05 vs after CPAP.

2p<0.05 vs control and p<0.01 vs after CPAP.

---

**Figure 1.** Uric acid excretion in 10 control subjects and 20 patients with OSAHS before and after therapy with nasal CPAP. Shaded areas represent mean±SEM.
The usefulness of measuring uric acid excretion in patients with OSAHS lies more in outpatient management than in diagnosis. With respect to diagnosis, future studies of large numbers of subjects are needed to perhaps define a threshold. However, once the level of uric acid excretion has been determined in a given patient with OSAHS after CPAP treatment, the measurement can be repeated periodically to determine the success of long-term CPAP therapy or to assess patient compliance. This would be useful particularly for the management of patients who do not have easy access to health-care facilities and sleep laboratories. However, additional research is needed before any guidelines can be established.

ACKNOWLEDGMENT: The author thanks Dr. Shahrokh Javaheri for his assistance in the performance and interpretation of sleep studies.

REFERENCES

1 Fox IH. Metabolic basis for disorders of purine nucleotide degradation. Metabolism 1981; 30:616-34
6 Fox AC, Reed GE, Meilmam H, et al. Release of nucleosides from canine and human hearts as an index of prior ischemia. Am J Cardiol 1979; 43:52-58
8 Jensen MH. The catabolism of purine nucleotides in the human organism [thesis]. Institute of Anaesthesiology, Odense University. Odense, Denmark: CAVI Bogtrykkeri, 1986
17 Ferris BG. Recommended standardized procedures for pulmonary function testing. Am Rev Respir Dis 1978; 118:55-88
22 Tietz NW. Clinical guide to laboratory tests. 2nd ed. Philadelphia: W.B. Saunders, 1990: 568
32 Lin CC, Tsan KW, Lin CY. Plasma levels of atrial natriuretic factor in moderate to severe obstructive sleep apnea syndrome. Sleep 1993; 16:37-39