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Renin–angiotensin–aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism


Key words: obstructive sleep apnoea, primary aldosteronism, renin-angiotensin-aldosterone system

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Abstract
Obstructive sleep apnoea (OSA) is a sleep disorder characterized by recurrent episodes of oxygen desaturation during sleep, representing an independent risk factor for cardiovascular disease, such as myocardial infarction, stroke, congestive heart failure and resistant hypertension. Several neurohormonal mechanisms have been suggested to account for blood pressure increases, such as sympathetic nervous system hyperactivity, oxidative stress, renin–angiotensin–aldosterone system (RAAS) activation, endothelin system activation, and endothelial dysfunction. The aim of this study was to evaluate the behaviour of RAAS and the prevalence of primary aldosteronism (PA) in these patients and possible correlations between RAAS and the severity of OSA. From October 2007 to November 2008 we studied 325 consecutive newly diagnosed hypertensive patients; 71 patients (21.8%) presented with clinical signs of sleep disorders, evaluated also through a specific questionnaire (Epworth Sleepiness Scale). In hypertensive patients with sleep disorders, 53 patients were affected by OSA; in this group 18 patients were affected by PA (five with aldosterone-producing adenoma (APA) and 13 with bilateral hyperplasia (IHA)); obesity was also demonstrated (BMI > 30 kg/m²). Overall, in patients with OSA PRA levels correlated positively with apnoea/hypopnoea index (AHI; \( r = 0.35, p < 0.01 \)), and in all groups the waist circumference and the neck circumference were correlated positively with AHI (\( r = 0.3, p < 0.02 \) and \( r = 0.3, p < 0.03 \), respectively). We revealed a high prevalence of PA in patients with OSA, and we can conclude that patients with hypertension and OSA, especially those who are newly diagnosed, must be evaluated for PA.

Introduction
Obstructive sleep apnoea (OSA) is characterized by recurrent episodes of partial or complete obstruction of the upper airways during sleep resulting in oxygen desaturation and arousal from sleep. OSA is an independent risk factor for cardiovascular disease, including myocardial infarction, stroke, congestive heart failure and arterial hypertension. Approximately 50–60% of patients with OSA are hypertensive, and it is estimated that 50% of these hypertensive patients have multi-drug-resistant hypertension.

A variety of neurohormonal mechanisms have been suggested to account for blood pressure increases in patients with OSA, such as sympathetic nervous system hyperactivity, oxidative stress, renin–angiotensin–aldosterone system (RAAS) activation, endothelin system activation, and endothelial dysfunction.

The aim of this study was to evaluate: (1) the behaviour of the RAAS in patients with OSA; (2) the prevalence of primary aldosteronism (PA) in these patients; and (3) the possible correlations between RAAS and severity of OSA.

Material and methods
We studied 325 consecutive newly hypertensive patients who were referred to the Day Hospital of Internal Medicine and Secondary Hypertension, Department of Clinical Sciences, University of Rome ‘Sapienza’, Italy, from October 2007 to November 2008. Some 254 hypertensive patients did not have any features of sleep disorders (154 male, 100 female; mean age 50.8 ± 7.5 years), and 71 patients (21.8%; 51 male, 20 female; mean age 51.5 ± 9.7 years) presented with clinical signs of sleep disorders (Table 1). The excessive daytime sleepiness was evaluated by the use of a specific questionnaire, the Epworth Sleepiness Scale. If the score was equal to or greater than 10, patients were referred to Centre for Diagnosis and Cure of Roncopathy, where they underwent polysomnography for the validation of OSA. Patients without a diagnosis of OSA were classified as habitual snorers.
Patients with renal insufficiency (creatinine > 1.4 mg/dl), acute or chronic bronchopulmonary disease, coronary artery disease, previous cerebrovascular events and arteriopathies were excluded from the study. Demographic and haemodynamic parameters were noted in all patients: body mass index (BMI), waist circumference, neck circumference (measured at the cricoid level), clinic and ambulatory blood pressure.

Diagnostic criteria
After 2 weeks of following a normal sodium (140–150 mmol/l) and potassium diet (40–50 mmol/l), fasting blood samples for plasma aldosterone (PAC) and plasma renin activity (PRA) were obtained in all individuals. Subjects were supine for at least half an hour. All anti-hypertensive drugs were withdrawn at least 3 weeks (up to 2 months for spironolactone) before haemodynamic, biochemical and hormonal evaluation.

In hypertensive patients in whom treatment could not be withdrawn for ethical reasons, calcium-channel blockers or α1-receptor blockers were utilized at doses required to achieve blood pressure control. These agents are considered to have a neutral effect on RAAS.

Diagnosis of PA was made as described previously.15 A cut-off PAC/PRA ratio of more than 40 (ng/dl/ng/ml/h) in the presence of aldosterone higher than 15 ng/dl and suppressed PRA was used as a screening test for PA. In the case of a PAC/PRA ratio greater that 40, patients underwent a saline infusion (0.9% NaCl 500 ml/h for 4 h) as a confirmatory test, and only those with PAC levels that failed to decrease to less than 5 ng/dl after the saline infusion were diagnosed as having PA. In these patients computed tomography, nuclear magnetic resonance scan of the adrenal glands or adrenal venous sampling were performed to differentiate between aldosterone-producing adenoma (APA) and bilateral hyperplasia (IHA). In all patients who underwent unilateral adrenalectomy, an adrenal adenoma was confirmed at surgery.

PRA was measured by radioimmunoassay (RIA) using commercial kits (RenCTK: Sorin Biomedica). Normal range sitting at rest, on a normal sodium diet, was 0.2–2.8 ng/ml/h; intra-assay and inter-assay coefficients of variation (CVs) were within 8% and 10%, respectively.

The assay for PAC was performed with diagnostic kits (Aldosterone Mirya, Technogenetics). Normal range was 1–15 ng/dl supine, 3–32 ng/dl upright on a normal sodium diet; intra-assay and inter-assay CVs were both < 5.6%; the cross-reactivity of the antibody for aldosterone for other adrenal steroids was < 0.001%.

Nocturnal polysomnography was performed in hospital (by MS), and included the recording of electroencephalography, electrooculography, electrocardiography, electromyography, SaO2 (oxygen meter), breath sounds (tracheal microphone), chest wall and abdominal movements (respirator), and nasal/oral airflow (thermistor). A 6-h minimum duration was required for diagnosis. Data obtained included sleep efficiency, number and duration of apnoea/hypopnoea episodes, apnoea/hypopnoea index (AHI), the number of desaturations greater than 4% below baseline, and the final diagnosis. Apnoea was defined as cessation of airflow greater than 10 s. Hypopnoea was defined as a recognizably, transient reduction, but not complete cessation of breathing greater than 10 s and associated with desaturation greater than 4% below baseline, cortical arousal, or both. The AHI represents the sum of all apnoeas and hypopnoeas for an hour. OSA was defined as AHI greater than 5, as all patients undergoing polysomnography were symptomatic. Patients were divided into groups according to severity of the disease (mild OSA = AHI from 5–15; moderate OSA = AHI ranging from 15–30; and severe OSA = AHI > 30.17

Statistical analysis
All data are expressed as mean ± standard deviation (M ± S). Statistical analysis was performed by using Sigmastat Software (Jandel Corporation), and all values were analysed with analysis of variance (ANOVA), followed by Student’s t-test whenever appropriate. The correlation between various parameters was done using Spearman single linear correlation. Post-hoc pairwise comparisons were made with Tukey’s adjustment for multiple comparisons. A p-value less than 0.05 was considered significant. Chi-square test was performed to evaluate differences in median values between studied groups.

Results
Demographic data are reported in Table 2. Altogether 254 hypertensive patients without sleep disorders and 71 hypertensive patients with sleep disorders were enrolled in the study; 18 (25.4%) patients were identified as habitual snorers and 55 (74.6%) patients were identified as affected by OSA. In the hypertensive patients without sleep disorders 25 subjects were affected...
### Table 1
Baseline characteristics of subjects.

<table>
<thead>
<tr>
<th></th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Neck Circumference (cm)</th>
<th>Waist Circumference (cm)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>HR (bpm)</th>
<th>Prevalence PA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive patients without sleep disorders (n = 254)</td>
<td>154/100</td>
<td>50.8 ± 7.5</td>
<td>29.8 ± 3.5</td>
<td>35.7 ± 3.2</td>
<td>102.1 ± 8.5</td>
<td>140.5 ± 15.5</td>
<td>85.5 ± 7.5</td>
<td>75.2 ± 8.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Hypertensive patients with sleep disorders (n = 53)</td>
<td>35/18</td>
<td>50.9 ± 7.6</td>
<td>31.6 ± 4.2</td>
<td>41.8 ± 4.2</td>
<td>107.2 ± 10.2</td>
<td>143.7 ± 14.5</td>
<td>87.8 ± 9.1</td>
<td>72 ± 8.6</td>
<td>25.4</td>
</tr>
<tr>
<td>p-value</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

AHI: apnoea/hypopnoea index, BMI: body mass index, DBP: diastolic blood pressure, OSA: obstructive sleep apnoea patients, PA: primary aldosteronism, SBP: systolic blood pressure.

### Table 2
Baseline characteristics of different studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>AH1 (n/h)</th>
<th>BMI (kg/m²)</th>
<th>Neck Circumference (cm)</th>
<th>Waist Circumference (cm)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snorers (n = 18) Group (1)</td>
<td>14/4</td>
<td>48.3 ± 6.9</td>
<td>1.5 ± 1.2</td>
<td>30.3 ± 4.3</td>
<td>41.9 ± 4.4</td>
<td>102.3 ± 11.6</td>
<td>142.5 ± 12.3</td>
<td>88.6 ± 5.9</td>
<td>73.4 ± 10.4</td>
</tr>
<tr>
<td>OSA (n = 35) Group (2)</td>
<td>22/13</td>
<td>51.1 ± 10.1</td>
<td>25.1 ± 19.04</td>
<td>33.41 ± 5.5</td>
<td>42.6 ± 4.2</td>
<td>109.6 ± 13.9</td>
<td>142.7 ± 17.7</td>
<td>88.6 ± 9.3</td>
<td>73.5 ± 8.9</td>
</tr>
<tr>
<td>PA + OSA (n = 18) Group (3)</td>
<td>15/3</td>
<td>55.2 ± 10.5</td>
<td>21.89 ± 17.2</td>
<td>33.26 ± 2.97</td>
<td>44.3 ± 4.5</td>
<td>111.2 ± 6.4</td>
<td>150.6 ± 18.8</td>
<td>93.3 ± 11.2</td>
<td>71.7 ± 8.7</td>
</tr>
</tbody>
</table>

p-value: p < 0.02 (1) vs (3)  p < 0.001 (1) vs (3)  p < 0.02 (1) vs (3)  p < 0.001 (1) vs (3)  p < 0.04 (1) vs (2)  p < 0.06 (1) vs (2)  

AHI: apnoea/hypopnoea index, BMI: body mass index, DBP: diastolic blood pressure, OSA: obstructive sleep apnoea patients, PA: primary aldosteronism patients, SBP: systolic blood pressure.
by PA, whereas 18 patients with OSA had PA (5 with APA and 13 with IHA).

All 71 patients were obese (BMI > 30 kg/m²) with an increased waist circumference (WC: > 88 cm in women and > 102 cm in men); patients with PA + OSA and with OSA only presented with higher WC (111.2 ± 6.4 cm and 109.6 ± 13.9 cm) than habitual snorers (102.3 ± 11.6 cm) (Figure 1).

As shown in Table 3, serum potassium levels were lower in patients with PA + OSA with respect to the other two groups (3.86 ± 0.4 mEq/l versus 4.06 ± 0.4 mEq/l versus 3.86 ± 0.4 mEq/l; p < 0.02 and p < 0.05, respectively).

PAC and PRA levels were significantly higher in patients with PA + OSA with respect to other patients (PAC 43.75 ± 13.61 ng/dl versus 26.21 ± 16.08 ng/dl versus 29.2 ± 10.64 ng/dl; p < 0.001, respectively). In all patients with OSA, PRA levels correlated positively with AHI (r = 0.35; p < 0.01) (Figure 2), also after adjustment for BMI and WC.

### Conclusion

OSA is a common disorder in which repetitive apnoea exposes the cardiovascular system to cycles of hypoxia, exaggerated intra-thoracic pressure, and arousals. This is a condition that affects 9–25% of the adult population, and untreated OSA represents an independent risk for hypertension, myocardial ischaemia and stroke.

However, the mechanisms underlying the association between OSA and cardiovascular factor risk, such as hypertension, are not well understood. Most recently it has been hypothesized that an excess of aldosterone could be caused by OSA, although limited by a small sample size, our results indicate that PA is a frequent finding among patients with sleep disorders, particularly among patients with OSA. In particular, of 71 hypertensive patients with sleep-disordered breathing enrolled in the study, 25.4% were habitual snorers and 74.6% were affected by OSA. In this group 18 patients were affected by PA, five had APA and 13 had IHA.

PA was described by Conn in 1955 and is much more common than had been historically believed, with a prevalence among general hypertensive patients of approximately 5–20%. Recently, in the Primary Aldosteronism Prevalence in Italy (PAPY) Study, a prospective survey of 1180 consecutive newly diagnosed hypertensive patients referred to specialized hypertension centres, APA...
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Biochemical metabolic parameters and renin-angiotensin-aldosterone system (RAAS) in all groups study.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting glucose (mg/dl)</td>
</tr>
<tr>
<td>Snorers (n=18) Group (1)</td>
<td>100.4 ± 18.3</td>
</tr>
<tr>
<td>OSA (n=35) Group (2)</td>
<td>99.3 ± 12.4</td>
</tr>
<tr>
<td>PA + OSA (n=18) Group (3)</td>
<td>101.2 ± 18.7</td>
</tr>
<tr>
<td>Saline Infusion Test</td>
<td></td>
</tr>
<tr>
<td>Snorers (n=18) Group (1)</td>
<td></td>
</tr>
<tr>
<td>OSA (n=35) Group (2)</td>
<td></td>
</tr>
<tr>
<td>PA + OSA (n=18) Group (3)</td>
<td></td>
</tr>
</tbody>
</table>

and IHA were found in 4.8% and 6.4% of all patients, an overall prevalence of APA of almost 11%. In a general practice study of 125 patients, approximately 1 in 10 patients had presumed PA, determined by elevated plasma aldosterone–renin ratios. The prevalence increases progressively with the severity of hypertension. In patients with mild hypertension, the prevalence was found to be only 2%, which is not different from normotensive subjects. In patients with moderate hypertension the PA prevalence was 8% and in patients with severe hypertension the prevalence was 13%. PA is particularly common in patients with resistant hypertension (defined as blood pressure that remains above goal despite the use of three anti-hypertensive medications in effective doses), and according to recent evidence the prevalence of PA may be higher at approximately 20%.

The relationship between OSA and PA has been reported by some authors. Colhoum et al., in a group of patients referred for resistant hypertension and high risk for OSA, reported that 26 of 72 patients (36%) received a diagnosis of PA; in contrast 8 of 42 patients (10%) with low risk of OSA, received a diagnosis of PA. In our study we confirmed in all PA patients the presence of OSA via polysomnography, using a partially different definition of PA. In fact, Colhoum et al. defined PA as a suppressed PRA (< 1 ng/ml/h) and elevated 24 h urinary aldosterone excretion (> 12 µg) in the setting of high dietary sodium ingestion (> 200 mEq/24 h). We defined PA as a PAC/PRA ratio greater than 40 (PAC ng/dl: PRA ng/ml/h) in the presence of PAC higher than 15 ng/dl and suppressed PRA (< 0.1 ng/ml/h), and confirmed by saline infusion (0.9% NaCl 500 ml/h) with PAC decreased to less than 5 ng/dl. In general, a high ratio (PAC/PRA) is meaningful only when PAC exceeds 15 ng/dl.

The nature of the association between OSA and PA is at present unknown. It is possible that aldosterone excess may contribute to OSA through increased oedema of nasopharyngeal tissues. Pimenta et al. hypothesize that increased sodium and water retention, secondary to hyperaldosteronism, may contribute to tissue oedema in the upper respiratory tract, leading to obstruction of the airway and worsening OSA.

A further result of our study is represented by the significant correlation between PRA levels and AHI values in patients with OSA. The AHI is the common parameter used to assess the severity of sleep-disordered breathing (mild OSA = AHI ranging from 5–15; moderate OSA = AHI ranging 15–30; severe OSA = AHI > 30) and reflects various components of OSA because the definition of hypopnoea includes desaturation and/or arousal. The relationship between RAAS activation and OSA is complex and remains to be elucidated. In animals, a combination of acute hypercapnoea and hypoxia increases PRA and PAC. Maillard and coworkers reported that in seven normotensive subjects with OSA night time PAC levels were lower in contrast to PRA levels, that were generally the same in OSA patients versus non-OSA control subjects. Moreover, activation of the renin–angiotensin system by recurrent hypoxia may contribute to elevation of blood pressure in OSA patients. Indeed, Fletcher et al. demonstrated an increase in mean arterial pressure in rats exposed to intermittent hypoxia.
akin to that seen in OSA and the attenuation of this response by an AT1 receptor inhibitor.

Finally, in our study we confirmed that central obesity and neck circumference increased with severity of OSA evaluated with AHI. WC reflects both abdominal subcutaneous adipose tissue and abdominal visceral adipose tissue, and is a general index of central adipose mass. Central obesity is an independent risk factor for OSA, probably because of the deposition of fat around the neck and submental region making the upper airway prone to collapse when lying supine.\textsuperscript{30,31} and upper body obesity also reduces lung volumes.\textsuperscript{30,31} Central obesity, which generates fat distribution particularly at the abdominal level, upper body and neck, is the type most associated with OSA.\textsuperscript{30,41} Compared with normal individuals, obese OSA subjects show 42\% more fat in their cervical region,\textsuperscript{42} which causes pharyngeal lumen narrowing and results in increased risk of developing OSA.\textsuperscript{43} Some studies have shown that body weight loss is related to an increase in airway transversal diameter,\textsuperscript{44} which could result in AHI improvement.

In conclusion, we confirmed a high prevalence of PA in patients with OSA and demonstrated overall in patients with OSA a positive correlation between PRA and OSA severity. These results indicate that patients with hypertension and OSA should be investigated for PA.

References


