Sleep Medicine 16 (2015) 101–106

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Plasma renin levels and renin–blood pressure relationship in normal-weight and overweight children with obstructive sleep apnea and matched controls

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ARTICLE INFO

Article history:
Received 6 November 2013
Received in revised form 20 May 2014
Accepted 22 May 2014
Available online 27 August 2014

Keywords:
Children
Obstructive sleep apnea
Blood pressure
Renin
Obesity
Hypertension

ABSTRACT

Background: Obstructive sleep apnea (OSA) has been increasingly linked to elevated blood pressure (BP) and hypertension. Repeated night-time hypoxia in OSA is associated with activation of two critical mechanisms of BP control: the autonomic nervous system and the renin–angiotensin system (RAS). The effects of OSA on the RAS are not well understood, especially in children. We hypothesized that children with OSA have elevated renin levels and abnormal relationships between BP and renin.

Methods: Polysomnography was conducted in 173 children to diagnose OSA (apnea–hypopnea index [AHI] >1 event/h) and control (AHI ≤1 event/h) groups. Age- and gender-specific *z*-scores for body mass index (BMI) were calculated to divide subjects into obese (BMI ≥95%), overweight (BMI ≥85% and <95%) and normal-weight (BMI <85%) groups. Morning BP was measured with an automatic sphygmomanometer and venous blood samples were collected for measurements of plasma renin, after overnight polysomnography.

Results: Plasma renin levels were not significantly different in all four groups after adjustment of age, gender, and race. Significantly negative associations between renin and BP were present only in the normal-weight control group and were absent in the other three groups.

Conclusion: Plasma renin levels were not significantly increased in children with OSA compared to controls for both normal-weight and overweight subjects. The absence of normal, negative renin–BP relationships in both overweight and OSA children suggests a dysfunction of the RAS, which could be a mechanism for increased BP and the development of hypertension.

1. Introduction

Obstructive sleep apnea (OSA) has been increasingly linked to cardiovascular diseases [1]. In children with OSA, blood pressure (BP) is elevated not only during sleep apnea events at night, but also during daytime wakefulness while breathing normally [2–5]. Hypertension [6] and drug-resistant hypertension [7] are widespread in the middle-aged adult population with OSA. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identified OSA as the most prevalent among identifiable causes of hypertension [8]. Experimental animal models of OSA have a significant increase in BP that is normalized after elimination of OSA [9]. In clinical studies, successful treatment of OSA significantly reduced BP in hypertensive patients with OSA [10–13]. These studies provide compelling evidence of a causal relationship between OSA and hypertension. However, the pathophysiologic mechanism of elevated BP and mechanisms for the development of hypertension in OSA patients are poorly understood.

Repeated night-time apneic events during sleep in OSA patients are associated with hypoxemia and frequent arousals that cause sleep disturbance and sleep fragmentation [14]. Hypoxemia and partial sleep loss in OSA patients are strongly associated with sympathetic neural activation [15], oxidative stress [16], inflammation [17], coagulation [18], endothelial dysfunction [19], and metabolic and hormonal dysregulation [20,21]. Markedly elevated sympathetic activity in patients with OSA is a well-recognized mechanism of increased BP that may cause development of neurogenic hypertension [22]. Recently published results of reduced baroreflex sensitivity [23] and impaired BP control [24] in children with OSA suggest an abnormality in the neural feedback regulation of BP that causes increased BP in children with OSA. Baroreflex dysfunction in these children may be a critical mechanism of increased BP, considering the significant improvement of baroreflex sensitivity after treatment of OSA with adenotonsillectomy [25].

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http://dx.doi.org/10.1016/j.sleep.2014.05.022
1389-9457/

The renin–angiotensin system (RAS) plays an important role in long-term BP regulation through maintenance of the extracellular fluid volume as a vasoconstrictor. Dysregulation of either the sympathetic nervous system or the RAS, or a combination of both, contributes to BP elevation and the development of hypertension. Although extensive data are available on the sympathetic mechanism of BP regulation in OSA [15], data on the RAS in adult patients with OSA are limited, and, to our knowledge, no data are available in children with OSA. Further, the results of previous studies on the RAS in adult OSA patients are controversial. Increased angiotensin II [26] and similar levels of renin and aldosterone [27,28] have been reported in OSA patients compared to matched controls. A significantly positive relationship between severity of OSA and plasma aldosterone in patients with resistant hypertension has also been reported [29]. The levels of plasma renin are associated with age [30], gender [31], obesity [32], sleep cycle [33], time of the day [34], and dietary salt intake [35]. Although obesity is an important risk factor for OSA, the effects of obesity on renin levels in children with OSA have not been studied. In normotensive children, plasma renin and aldosterone levels are negatively related to ambulatory BP measurements [36].

The present study aimed to examine the levels of plasma renin and their association with BP both in children with OSA and in healthy children who were either overweight or normal weight. We tested the hypothesis that OSA children, whether overweight or normal weight, would have increased plasma renin levels compared to their respective control groups matched for age, gender, and race and an altered negative association between BP and renin.

2. Methods

2.1. Subjects

Children aged 5–14 years were recruited from the Otolaryngology and Pediatric Clinic of Cincinnati Children's Hospital Medical Center for overnight polysomnography (PSG) for diagnosis of OSA. Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Age- and gender-specific *z*-scores for body mass index (BMI) were calculated using reference data available in the Centers for Disease Control and Prevention 2000 growth charts for the USA [37]. Children with OSA were divided by BMI percentile into normal-weight (BMI <85%), overweight (BMI ≥85% and <95%) and obese (BMI ≥95%) groups. Healthy control children (without OSA) matched for age, gender, race, and BMI percentile were also recruited for PSG. OSA subjects were free of cardiovascular, cerebrovascular, and any chronic medical disorders or genetic conditions, had never been treated for OSA, and either were on no medications or chronic asthma medications were temporarily discontinued for ≥24 h prior to the sleep study. Control subjects were free of any acute or chronic disease and on no medications. Signed informed consent and assent for children aged >7 years were obtained from each study participant before enrollment in the study. The study was approved by the Cincinnati Children's Hospital Medical Center Institutional Human Subjects Review Board.

2.2. Study design

A medical history was obtained and a physical examination was performed on all subjects before the sleep study. The presence and severity of OSA were determined by standard overnight PSG, including electroencephalography, electro-oculography, electromyography, finger-pulse oximetry, thermistor measurements of oronasal airflow, and measurements of rib-cage and abdominal movements of breathing. The presence of snoring was identified with recording of audio and vibration using a microphone taped on the throat of the subjects. All sleep studies were scored according to the standard criteria set by the American Thoracic Society and by the same board-certified sleep specialist.

Demographic data, heart rate, and BP were measured in the evening prior to the sleep study. All subjects awakened spontaneously in the early morning, and blood samples were collected and BP was measured while the subjects were on the bed in a supine position and prior to ambulation. Venous blood was collected for measurements of renin levels immediately after awakening. Supine BP was measured three times in the morning after the blood draw with an automatic sphygmomanometer (Dinamap; Critikon, Tampa, FL, USA), and averages of the three BP measurements were used for the statistical analyses.

2.3. Renin analysis

Plasma renin levels were determined by an immunoradiometric assay using Packard Cobra II Auto-Gamma Counter Model D5005 (Hewlett Packard, Meriden, CT, USA). In brief, a primary monoclonal antibody recognizing both the active and inactive forms of renin was used, followed by a secondary antibody labeled with ^{125}I that specifically recognizes the active form of renin. The assay involved the incubation of both standard (calibrated against the international reference preparation: WHO 68/356) and unknown sera in the presence of an excess of the first insolubilized antibody on the wall of polystyrene tubes followed by an excess of the second antibody. After a 3 h room-temperature incubation, the tubes were washed to remove unbound material to the solid phase. The amount of complex, bound radioactivity was measured in a gamma-counter. Results of the samples were determined directly from the standard curve. Sensitivity of the analysis was 1 pg/mL. Intra-assay variations were 3.6% for low sample and 1.8% for high sample. Inter-assay variations were 5.0% for low sample and 3.7% for high sample. Ranges of measurements were between 1 and 320 pg/mL.

2.4. Statistical analysis

Descriptive analyses were performed with calculation of means, standard deviations, and medians for continuous variables. Categorical variables were measured using proportions. Bivariate associations of continuous renin and BP variables (systolic, diastolic, and mean BP) were analyzed using Spearman correlation coefficients. An analysis of covariance model was used to compare groups for differences in renin levels (log-transformed) and morning values for diastolic, systolic, and mean BP. Age, gender, and race were included as covariates. Least-squares means were compared between groups of interest, using a multiple comparison adjustment based on simulation. Significance was set a priori at $\alpha = 0.05$. Analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Demography, hemodynamics, and sleep profile in OSA and control subjects

Demography, hemodynamics, and sleep profile were not significantly different in OSA and control for both normal-weight and overweight groups, except for arousal index (AI), respiratory disturbance index (RDI), apnea–hypopnea index (AHI), and percent of REM sleep (Table 1). In overweight children, AI, RDI, and AHI were significantly increased in OSA compared to control subjects. In normal-weight children, percent of REM sleep, RDI, and AHI were significantly increased in OSA compared to control subjects.