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Pupillometric findings in children with obstructive sleep apnea

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Abstract

Background—Obstructive sleep apnea (OSA) leads to intermittent hypoxia, activation of the sympathetic nervous system, and eventually cardiovascular morbidity. Alterations in autonomic nervous system (ANS) tone and reflexes are likely to play major roles in OSA-associated morbidities, and have been identified in a subset of children with OSA.

Objectives—To evaluate whether pupillometry, a noninvasive and rapid bedside test for the assessment of autonomic nervous system dysfunction (ANS), would detect abnormal ANS function in children with OSA.

Methods—Children ages 2-12 years underwent polysomnography (PSG), and were divided based on PSG findings into two groups; Habitual Snorers (HS; AHI <1 h/TST, n=17) and OSA (AHI>1 h/TST, n=49), the latter then sub-divided into AHI severity categories (>1 but <5, >5 but <10, and >10 h/TST). Pupillometric measurements were performed during the clinic visit in a dark room using an automated pupillometer device.

Results—A total of 66 subjects with a mean age of 7.3 ± 2.6 years were recruited. There were no statistically significant differences between any of the groups, even when comparing severe OSA (n=15) and HS in any of the measures related to pupillary reflexes. However, mild, yet significant increases in systolic blood pressure and morning plasma norepinephrine levels were detected in the severe OSA group.

Conclusion—Although ANS perturbation are clearly present in a proportion of children with OSA, particularly those with severe disease, pupillary responses do not appear to provide a sensitive method for the detection of ANS dysfunction in OSA children.

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Keywords

Obstructive Sleep Apnea; Pupillometry; Pediatrics; Autonomic Nervous system; Autonomic dysfunction; Sleep apnea; Norepinephrine

Introduction

Obstructive sleep apnea (OSA) is a common condition affecting 2-4% of the pediatric population. It is characterized by recurring events of partial or complete upper airway obstruction during sleep leading to disruption of sleep integrity, as well as gas exchange abnormalities (1). Upper airway obstruction during an apneic event results in increased negative intra-thoracic pressures to overcome the partially or completely occluded airway. As a result, both left ventricular transmural pressures and venous return to right ventricle increase, and can be accompanied by recurrent hypoxic events that raise the pulmonary pressure by inducing vasoconstriction in pulmonary circulation and therefore, increasing right ventricular afterload.(2) These episodic circulatory changes along with the direct effects of intermittent hypoxia ultimately lead to structural and functional remodeling of peripheral and central baroreceptors and chemoreceptors, with increased sympathetic tonic and reactive outflow and parasympathetic withdrawal (3). Furthermore, sleep fragmentation from repeated arousals also recruits the sympathetic nervous system, such that overall autonomic nervous system (ANS) imbalance occurs, and can be manifest well after the apneic events have ceased, i.e., during wakefulness. (3).

In contrast to the previous belief of “cardiovascular immunity” in children with OSA, there is now evidence that if left untreated, OSA during childhood may set the beginning of both immediate and long-term cardiovascular morbidities that may not become apparent till adulthood (4-6). Furthermore, it is currently believed that the underlying processes of such morbidity reside in ANS dysfunction (3, 7), and that the latter is also implicated in several other serious consequences of OSA such as cognitive deficits (8, 9) and insulin resistance (10, 11). Therefore, early detection of ANS abnormalities in children with untreated OSA may help to identify candidates who are at increased risk for developing morbidity, and thus provide them with timely and effective treatment. To this effect, alterations in ANS have been evaluated using different methodologies including heart rate variability (HRV), blood pressure (BP) and blood pressure variability (BPV) peripheral arterial tonometry, and catecholamine assays (12-16). However, a simple office-based test would be highly desirable.

The eye pupil reaction to light involves an afferent limb (i.e., cranial nerve II) and an efferent limb (i.e., cranial nerve III), and such reflex response is vital for visual adaptation to environmental light. Muscarinic receptors of the pupillary sphincter muscle represent the parasympathetic arm and stimulation of these receptors by acetylcholine (ACh) results in miosis, eliciting the initial response of the eye when exposed to a flash of light. Mydriasis occurs through activation α -adrenergic receptors in dilator muscles, which represent the SNS arm of the reflex. Patients with ANS dysfunction exhibit sympathetic or parasympathetic deficits in the pupillary responses to light, which makes assessment of

pupillary reflexes a potentially convenient and simple method for evaluation of ANS (17). Indeed, pupillometric measures have been explored in children with different medical conditions including congenital central hypoventilation (18) allergic rhinitis (19), nocturnal enuresis (20), connective tissue diseases (21), diabetes mellitus (22), as well as a correlate of sleepiness (23). A recent study in a small number of adults with OSA reported significant differences in pupillometric responses when compared to controls (24). Therefore, the aim of our study was to evaluate whether pupillometry, a noninvasive and rapid bedside test for the assessment of ANS would detect abnormal ANS function in children with OSA.

Methods

All children, ages 2-12 years, who were evaluated for clinical suspicion of OSA at the University of Chicago Pediatric Sleep Medicine Center were invited to participate in this study. The research protocol was approved by the University of Chicago internal review board (IRB) committee (protocol #09-115-B-CR005), and consent was obtained prior to the testing from all participants and their caregivers/parents. All subjects underwent an overnight polysomnography (PSG) and pupillometric testing. Pupillometric measurements were performed during the clinic visit, always conducted in the afternoon hours (1:00-4:00 PM), in a dark room using the NeurOptics PLR-2000 pupillometer device (see below).

All participants in this convenience sample underwent an overnight polysomnography at the Sleep Disorders Center at the University of Chicago Medicine as previously reported (25). Sleep studies were performed in two dedicated, quiet, dark rooms. No sleep deprivation or sedation was used. Children were studied for at least 8 hours in a quiet, darkened room with an ambient temperature of 24°C in the company of one of their parents using a commercially available data acquisition system (Polysmith; Nihon Kohden America Inc., CA, USA). The NPSG studies were scored according to the 2007 American Association of Sleep Medicine guidelines for the scoring of sleep and associated events (26). The proportion of time spent in each stage of sleep was calculated as a percentage of total sleep time (TST). A respiratory event was scored as an obstructive apnea if it was associated with a >90% fall in signal amplitude for >90% of the entire event compared to the baseline amplitude, the event lasted for at least two breaths and there was continued or increased respiratory effort throughout the period of the event. A mixed apnea was scored if inspiratory effort was absent in the initial part of the event, followed by resumption of inspiratory effort before the end of the event. A central apnea was scored if respiratory effort was absent throughout the duration of the event, the event lasted for at least two missed breaths and was associated with an arousal/awakening or a 3% desaturation. A hypopnea was scored if the event was associated with a 50% fall in amplitude of the nasal pressure transducer, lasted at least for two breaths and was associated with an arousal/awakening or 3% desaturation. The obstructive apnea-hypopnea index (AHI) was calculated as the number of apnea and hypopnea per hour of TST. Arousals were classified as either spontaneous or respiratory, and corresponding indices, namely the total arousal index (TAI) and the respiratory arousal index (RAI), were computed.

Catecholamine Assay

Fasting blood samples were collected the morning after PSG. Plasma was immediately separated by centrifugation and stored at -80°C till assay. Norepinephrine concentrations were measured using a solid phase competitive enzyme linked immunosorbent assay (ELISA) (Alpco diagnostics, Salem, NH). The ELISA sensitivity is 1.33 pg/ml with inter-assay and inter-assay coefficients of variability of 8.5% and 16.1%. All samples were assayed in duplicates and values were retained if they were within 10% of each other.

Pupillometry

Pupillometric measurements were taken after allowing at least for one minute of adaptation in a dark room. Subject was asked to focus on a small target at least 10 feet away with the eye that was not being tested. Head level was maintained straight and both eyes open during testing. To assess pupillometric responses, the NeuroOptics® PLR-2000™ pupillometer was used. This is a handheld optical scanner, which stimulates the eye with a flash of light, and captures and analyzes a rapid sequence of digital images to obtain a temporal measurement of the diameter of a human pupil. The system acquires images using a self-contained infrared illumination source and a digital camera. It analyzes the captured image data and displays a summary of the measurement in the LCD window. The following elements of the pupillary response were assessed by the NeuroOptics device: INIT and END represent the diameter of the pupil before the reflex and just at the peak of the reflex respectively and are shown in millimeters; DELTA is the amount of pupillary constriction (INIT-END/INIT) as indicated a percentage; reflex onset latency (LAT) represents the time of the onset of the reflex and is provided in seconds; average constriction velocity (ACV) and maximum constriction velocity (MCV) are shown as millimeters/second, The negative sign is meant to differentiate the constriction from dilation of the pupil. Both velocities refer to the constricting movement of the pupil diameter responding to the flash of light. Average dilation velocity (ADV) is the average pupillary velocity to dilate back to its initial resting size after having reached the peak of the constriction and is indicated in millimeters/second. Lastly, T75 represents the total time taken by the pupil to recover 75% of the initial resting pupil size after reaching peak constriction and it is measured in seconds.

Data Analysis

Data are reported as mean $\pm$ SEM unless otherwise stated. Comparisons between OSA groups and HS were assessed using Mann-Whitney U tests, analyses of variance followed by post-hoc tests, or non-parametric tests as appropriate (MedCalc Statistical Software version 14.10.2; MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014). A p value <0.05 was defined as indicating statistical significance.

Results

A total of 66 habitually snoring children who were referred for evaluation of suspected OSA with a mean age (7.6 ± 2.7 years, range: 2 -12 years), 52 % male, and BMI-z score (0.96 ± 0.73) were recruited to the study. Subjects were divided based on PSG findings into 3 groups: Control (OAHI ≤ 1 h/TST, n=17), mild-moderate OSA (OAHI >1 but <10 h/TST, n=34) and severe OSA (OAHI >10 h/TST, n=15). Table 1 shows the demographic,

anthropometric, and PSG characteristics of the 3 groups. There were no significant differences in age, gender, ethnicity, BMI z score across the groups. However, systemic systolic blood pressure values were higher in severe OSA children compared to HS ($p<0.04$). Similarly, significant differences emerged across groups for respiratory disturbance measures (e.g., AHI, nadir S_pO_2), but not for sleep architecture characteristics.

Pupillometric measures did not reveal any significant differences across the 3 groups (Table 2). However, morning plasma norepinephrine levels, obtained in a subset of the overall cohort, revealed significant increases in this catecholamine among the children with severe OSA ($p<0.01$ vs. HS; $p<0.02$ vs. mild-moderate OSA; Table 2).

Discussion

In our study, assessment of pupillometric measurements, which are putative reporters of sympathetic and parasympathetic autonomic nervous system functions, revealed no evidence of any detectable differences across the various pupillometric parameters between primary snorers and children suffering from polysomnographically documented OSA. Although measurable changes in autonomic nervous system tonic and responsive activation occur in pediatric OSA (12-16), as evidenced by mild, yet significant differences in systolic blood pressure values, as well as by increased norepinephrine levels among the more severely afflicted children, pupillometric assessments failed to detect such differences.

It is now readily accepted that altered ANS function plays major roles in OSA-associated morbidity. However, direct physiological testing of the ANS is difficult, and for the most part, requires invasive, uncomfortable, or labor intensive procedures that preclude their widespread implementation. Indeed, the most commonly used techniques for evaluation of the ANS encompass monitoring cardiovascular reflexes through heart rate variability or blood pressure responses to physiological stimuli such as the tilt test, urinary or plasma catecholamine levels, tests of sudomotor function, and microneurography (27-29). Additionally, non-invasive measures have been proposed using spectral or non-linear analyses of heart rate variability, and have revealed changes in sympathetic-parasympathetic balance in OSA (13, 30, 31). Furthermore, improvements in ANS function were documented in 18 children with OSA and successfully treated with adenotonsillectomy, as indicated by heart rate decreases across all stages of sleep and improved heart rate variability spectral measures (32). In another study, pulse arterial tonometry was employed in OSA children and controls to assess microcirculatory changes resulting from sympathetic reflexes elicited by vital capacity sighs and cold water immersion of the upper extremity (14). Increased sympathetic vascular reactivity during wakefulness was apparent in the OSA group, and suggested autonomic nervous system dysfunction (14).

Similar to the present study, children with OSA are at increased risk for manifesting higher systolic and diastolic blood pressures, even during daytime (12, 33-38). Furthermore, the presence of OSA is also associated with exaggerated blood pressure responses during implementation of the Ewing test battery (i.e., head-up tilt, Valsalva maneuver, and deep breathing tests). Indeed, positive associations between pressor responses and OSA severity

were reported, thereby supporting the presence of increased basal sympathetic activity during wakefulness in the context of pediatric OSA (16).

In concordance with the putative ANS perturbations elicited by OSA, several studies assessed urinary levels of catecholamines and have globally reported the presence of elevated concentrations that were primarily circumscribed to more severe disease (39-43). However, when heart rate variability and catecholamine levels were sampled overnight during PSG in preschool children, alterations in the high frequency domain of emerged, even in the absence of changes in catecholamine levels, suggesting that early childhood may represent a window of opportunity for effective treatment of OSA and autonomic dysfunction, i.e., before the latter settles in, and becomes potentially irreversible (15).

Notwithstanding the recent rapid advances and development of non-invasive ANS assessment tools, the overall ease and accessibility of pupil reflexes, whose characteristics are closely regulated by the ANS (17), seemed particularly well suited to a more widespread implementation of ANS evaluation in the context of children at risk for sleep-disordered breathing. However, the absence of any significant differences between children with OSA compared to HS in pupillometric measures obviously excludes this option from further consideration. We posit that the negative results reported herein could be ascribed to the relatively short and variable duration between the onset of OSA and pupillometric measurements, as ANS dysfunction may progress slowly, and become apparent only in the later stages of untreated OSA. Of course, since non-snoring controls with normal polysomnographic findings were not included in the study, the remote possibility exists that differences in pupillometric measurements would emerge if such controls had been included. However, our pupillometric findings in HS subjects and those reported by Patwari and colleagues in healthy controls (18) are remarkably similar and therefore would suggest that such potential limitation is unlikely to have contributed to the negative findings.

In summary, ANS dysfunction is clearly present in a proportion of children with OSA, and is likely involved as an important pathophysiologic mechanism underlying OSA morbid consequences. Although detecting abnormalities in ANS function using a simple bedside device could offer an attractive screening tool for OSA-induced ANS morbidity, pupillary response characteristics do not appear to provide a sensitive enough method in children with OSA.

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Highlights

- OSA in children is associated with altered autonomic nervous system function.
- Pupillometry provides a potential non-invasive bedside technique for assessment of autonomic nervous system function.
- Pupillometric measurements in children with OSA did not identify those children with elevated nor-epinephrine levels.

Table 1

Demographic and polysomnography characteristics of children with obstructive sleep apnea syndrome and habitual snorers with normal polysomnographic findings (HS).

	HS (n=17)	Mild to moderate OSA (n=34)	Severe OSA (n=15)	P value
Age (years) [Range]	7.8 ± 1.8 [4-11]	7.3± 2.4 [4-12]	6.9± 3.6 [3-11]	NS
Sex (male, %)	47	56	47	NS
Ethnicity (African American, %)	66.6%	63.6%	93.3%	NS
BMI-z score	0.99± 0.53	0.99± 0.60	0.85± 0.82	NS
BP systolic	103.7±7.4	105.8±8.5	113.2±7.9*	* - P<0.04 vs. HS
Stage	2.4± 1.8	5.1± 4.0	4.4± 3.5	NS
Stage 2 (%)	39.6± 16.7	46.0± 10.2	48.6± 5.9	NS
SWS (%)	27.6± 12.4	32.3± 11.8	24.7± 6.1	NS
REM (%)	19.2± 7.9	19.6± 7.2	22.1± 4.9	NS
Sleep efficiency (%)	88.4± 9.6	90.8± 10.2	89.9± 7.7	NS
Sleep latency (min)	24.6± 12.8	22.4± 25.8	17.8± 15.8*	* - P<0.04 vs. HS
Total sleep time (min)	393.1± 107.3	413.3± 71.4	410.0± 58.7	NS
Apnea-hypopnea index (events/h TST)	0.4 ± 0.2	4.4±2.6*	23.7±15.7*, ¥	* - P<0.01 vs. HS ¥ - P<0.01 vs. mild-moderate OSA
Total Arousal Index(events/h TST)	9.4± 3.2	13.6± 4.3*	21.5± 9.2*, ¥	* - P<0.01 vs. HS ¥ - P<0.01 vs. mild-moderate OSA
S _p O ₂ nadir (%)	93.3± 2.5	91.2± 16.5*	75.5± 12.3*, ¥	* - P<0.01 vs. HS ¥ - P<0.01 vs. mild-moderate OSA
Mean P _E TCO ₂ mmHg	38.4± 1.5	41.6± 1.5	42.8± 2.3*	* -P<0.04 vs. HS

OSA, obstructive sleep apnea; BMI-Z, body mass index z score; TST, total sleep time; SWS, slow wave sleep; REM, rapid eye movement sleep; S_pO₂, oxygen saturation by pulse oximetry; P_ETCO₂, end tidal CO₂

Table 2

Pupillometric measurements in children with obstructive sleep apnea syndrome and habitual snorers with normal Polysomnographic findings (HS).

	HS	Mild-Moderate OSA	Severe OSA	P value
INIT max diameter (mm)	6.29 ± 1.05	5.95 ± 0.99	6.1 ± 0.68	NS
END min diameter (mm)	4.48 ± 0.92	4.25 ± 0.75	4.32 ± 0.62	NS
DELTA	-29.2 ± 5.85	-28.48 ± 5.87	29.33 ± 4.47	NS
LAT (sec)	0.22 ± 0.04	0.21 ± 0.03	0.22 ± 0.04	NS
ACV (mm/sec)	-3.71 ± 0.74	-3.80 ± 0.72	3.78 ± 0.62	NS
MCV (mm/sec)	-5.11 ± 0.98	-4.96 ± 0.87	5.03 ± 0.90	NS
ADV (mm/sec)	1.27 ± 0.32	1.29 ± 0.35	1.26 ± 0.27	NS
T75 (sec)	2.39 ± 0.98	2.35 ± 1.10	2.29 ± 1.03	NS
Plasma norepinephrine (pg/mL)	87.4 ± 14.7 (n=13)	96.3 ± 17.2 (n=22)	169.5 ± 29.6* (n=13)	* - P<0.01 vs. HS

OSA, obstructive sleep apnea; INIT max, diameter of the pupil before the reflex; END min, the diameter of the pupil just at the peak of the reflex; DELTA, amount of the constriction (INIT-END)/INIT; LAT, latency represents the time of the onset of the reflex; ACV, average constriction velocity; MCV, maximum constriction velocity; ADV, average pupillary dilatation velocity; T75, total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction.