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Original Article

Obstructive sleep apnea in children is associated with severity-dependent deterioration in overnight endothelial function

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ABSTRACT

Background: Restorative sleep is expected to promote improved endothelial function (EF) in the morning compared to the evening. However, in adults with obstructive sleep apnea (OSA) EF is not only adversely affected, but it worsens during the night. Data in pediatric OSA are scarce, and overnight changes have not been explored. Therefore, we sought to examine potential associations between pediatric OSA and overnight changes in EF.
Methods: 59 habitually snoring children with various degrees of sleep-disordered breathing (age range, 4–16 years) underwent EF assessment (reactive hyperemia test by EndoPAT, Itamar Medical, Israel) in the evening before and the morning after an overnight polysomnography (PSG). Two brachial occlusion periods (1 min and 5 min) also were tested. Potential associations between evening-to-morning changes in EF and polysomnographic parameters were explored.
Results: Evening-to-morning changes in children with OSA displayed severity-dependent deterioration of EF, and occlusions lasting 1 or 5 min during the reactive hyperemia test yielded similar findings.
Conclusions: In children deterioration in EF during the night significantly correlated with the severity of OSA. Furthermore, the reactive hyperemia test can be reliably performed with only 60 seconds of arterial flow occlusion in children. These findings support our hypothesis that similarly to adults, sleep apnea in children results in endothelial dysfunction (ED). We speculate that pediatric OSA is less commonly associated with cardiovascular complications possibly due to the shorter duration of the syndrome.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent condition in children that is independently associated with an increased risk for systemic hypertension and cardiovascular disease [1]; OSA also alters lipid and metabolic homeostasis [2]. The intermittent increases in upper airway resistance during sleep lead to recurrent oxyhemoglobin desaturations, elevated carbon dioxide levels, sleep fragmentation, sympathetic activation, recurrent intrathoracic pressure swings, and reduced sleep efficiency [3–6].

Endothelial dysfunction (ED), an early risk marker for cardiovascular disease, frequently is present in adult and pediatric patients with OSA [7–11]. Indeed, work from our laboratory has illustrated that ED, as assessed by a modified hyperemic test after cuff-induced occlusion of the brachial artery, is more likely to be present among nonobese children ages 6 to 9 years who were diagnosed with OSA syndrome when compared to matched controls [11]. Additionally, the presence of obesity and OSA contribute to the magnitude of ED lending support to the concept that both conditions may adversely impose incremental long-term cardiovascular risk [12–14]. In addition, some of the variance in endothelial function (EF) has been ascribed to circulating endothelial progenitor cells [15], and abnormalities in postocclusive reperfusion responses are reversed when adequate and effective treatment of the underlying OSA syndrome is administered [11,16].

In recent years, a novel approach based on peripheral arterial tonometry (PAT) has been advanced as providing an automated, reproducible, and reliable method for assessment of EF and future cardiovascular risk in adults [17–21]. In children more severe morning EF is observed utilizing this technology in patients with diabetes mellitus type 1 with suboptimal control of their glycemic levels [22]. This technology has two important advantages over other technologies: (1) automatic software-driven analyses (no intra- and inter-observer variability) and more importantly

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(2) controlling for systemic autonomic changes during the study by measuring PAT changes during the test in both the occluded and the nonoccluded arms. In addition PAT has potential advantages relative to the ease of testing and as such, in the implementation of routine assessment of EF in children. However, occasionally the 5-min occlusion causes arm pain is intolerable in children. Thus, we aimed at testing reactive hyperemia following either 5 min or 1 min of brachial arterial occlusion and to test if these two different brachial occlusion times would differentially modify our findings on the hyperemic response. We hypothesized that children with OSA would display severity-dependent alterations in evening-to-morning EF changes as assessed by the reactive hyperemia test.

2. Methods

Consecutive otherwise healthy, habitually snoring children ages 4–16 years were referred for evaluation for suspected OSA and were recruited to investigate EF in two pediatric sleep centers, namely Comer Children's Hospital in Chicago, IL, USA and Rambam Medical Center, in Haifa, Israel. All methods outlined in our study were approved by the University of Chicago Human Research Committee and by the Institutional Review boards of Rambam Medical Center. Inclusion criteria consisted of any child suspected of OSA ages 4 to 17 years and the absence of any of the exclusion criteria delineated below. All participants underwent baseline overnight polysomnography (PSG), and their EF was assessed both in the evening and in the morning following the sleep study in the laboratory.

2.1. Exclusion criteria

All children who were found to be hypertensive (with either a systolic or diastolic blood pressure index >1) or those who were using antihypertensive therapies, were excluded. Furthermore, children with diabetes mellitus (fasting serum glucose, $\geqslant$120 mg/dL), with a craniofacial, neuromuscular, or defined genetic syndrome as well as children on long-term anti-inflammatory therapy or with any known acute or chronic illness, were excluded. In addition, children placed on sympathomimetic agents such as psychostimulants were not tested.

2.2. Measurements and testing

2.2.1. Anthropometry

Children were weighed on a calibrated scale and their weights were recorded to nearest 0.1 kg. Height (to 0.1 cm) was measured with a stadiometer (Holtain, Crymych, UK). Body mass index (BMI) was calculated and BMI *z* score was computed using Centers for Disease Control and Prevention 2000 growth standards (www.cdc.gov/growthcharts) and online software (www.cdc.gov/epiinfo). A BMI *z* score of >1.65 (>95th percentile) was considered as fulfilling obese criteria.

2.2.2. Sphygmomanometry

Arterial blood pressure was noninvasively measured in all children using an automated mercury sphygmomanometer (Welch Allyn, NY) at the brachial artery with a guidelines-defined appropriate cuff size on the nondominant arm [23]. Blood pressure measurements were made in the evening prior to commencement of nocturnal PSG and in the morning immediately after awakening. Systolic and diastolic blood pressure indices were calculated by dividing the average systolic and diastolic pressure by the respective 95th percentile for blood pressure (www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm) computed for age, gender, and height. Hypertension was defined by a systolic or a diastolic blood pressure index exceeding one and led to exclusion from the study.

2.2.3. Overnight PSG

PSG was conducted and scored as previously reported [24–27]. The diagnosis of children with OSA was defined by the presence of an obstructive apnea ($\geqslant$1/h) of total sleep time (TST) and an obstructive apnea–hypopnea index (AHI) $\geqslant$5 per hour of TST, respectively, and a nadir oxyhemoglobin saturation <92% [26]. Children with AHI <1 per hour of TST and no oxygen desaturations events during sleep were considered as controls. OSA was further subdivided into mild (1 < AHI; <5/h of TST), and moderate to severe (1 < AHI; >5/h TST).

2.2.4. Endothelial function

EF was assessed using two different approaches based on a modified hyperemic test induced by either 1- or 5-min cuff-induced occlusion of the radial and ulnar arteries by placing the cuff over the wrist. Children were in the sitting position throughout testing, and resting baseline PAT signals were acquired. Finger pulse wave amplitude was recorded with the EndoPAT (Itamar Medical Ltd., Caesarea, Israel). EndoPAT is a noninvasive technology that captures a beat-to-beat plethysmographic recording of the finger arterial pulse wave amplitude with pneumatic probes [28]. The PAT finger probe consists of a thimble-shaped sensor cap that imparts a uniform pressure field and exhibits a clamplike effect on the entire surface of the distal phalanx and measures pulsatile volume changes. PAT applies a significant counterpressure (60 mmHg) on the digit and avoids distal venous distention, thereby inhibiting venous pooling and blood stasis which could otherwise induce a venoarteriolar reflex vasoconstrictor response. The pressure field applied to the finger also may protect against local venous distension related to elevated venous pressure in the upper arm during the cuff inflation portion of reactive hyperemia testing [28]. PAT is therefore configured to unload arterial wall tension and increase the range of arterial wall motion without inducing potentially confounding vasomotor changes. The finger probe is connected by flexible tubing to isolated volume reservoirs that buffer pressure changes within the probes. The pressure change signals are then filtered, amplified, displayed, and stored for further analysis.

PAT probes were placed on one finger of each hand (occluded and control arms) for continuous recording of the PAT signal. After a 5- to 8-min equilibration period, which was used as baseline, the blood pressure cuff was inflated to suprasystolic pressures ($\geqslant$200 mmHg) for 1 or 5 min. The cuff was then abruptly deflated, while PAT recording continued for 5 min. The main outcome measure, the reactive hyperemia index, was calculated as (1) the ratio of the digital pulse volume during reactive hyperemia over a 1-min time interval starting 1 min after cuff deflation to that at baseline for 5-min occlusion periods [28] and (2) as the changes in reactive hyperemia index over the initial 30 s after deflation for occlusions lasting for 1 min to mimic the endothelial capillary responses previously determined using laser-Doppler flowmetry [13,14]. Of note the occlusion time of 60 s was chosen in the Chicago population based on the previous validation steps conducted in children with laser-Doppler technology and to minimize discomfort for the child [11,29]. Conversely, the 300-s occlusion was selected (in the Haifa population) to mimic the usual and optimized procedure performed in adult and adolescent participants [8,22,30].

2.3. Data analysis

Results are presented as mean ± standard deviation, unless otherwise stated. All numerical data were subjected to statistical analysis using independent Student *t* tests or analysis of variance

Table 1
Demographic characteristics and arterial blood pressure measurements in 59 children subdivided based on the occlusion duration used in endothelial function assessments.

Factor	1-Min occlusion time	5-Min occlusion time
N	32	27
Age	8.3 ± 2.1	10.6 ± 2.8
Boys	21 (66%)	23 (85%)
BMI	21.3 ± 6.1	20.6 ± 8.1
BMI *z* score	1.29 ± 1.09	1.15 ± 1.09
Obese (BMI *z* score $\geqslant$1.65)	13 (41%)	9 (33%)
Mean systolic blood pressure (mmHg)	96.9 ± 6.8	106.0 ± 12.4
Mean diastolic blood pressure (mmHg)	62.5 ± 5.8	67.0 ± 8.9

Abbreviation: BMI, body mass index.

followed by post hoc tests when appropriate using SPSS (version 17.0; Chicago, IL). For correlation analyses linear regression equations were employed. No variance stabilizing transformations were undertaken. A 2-tailed $p < 0.05$ was considered to define statistical significance.

3. Results

In total 59 children fit the initial inclusion criteria and were recruited into the study. Of these 17 had AHI <1 per hour TST, and the remainder fulfilled criteria for OSA. Thirty-two children had occlusion times of 60 s and 27 children underwent endothelial assessments with occlusions lasting for 5 min. There were no differences in age, gender, BMI, proportion of children fulfilling obesity criteria, or in blood pressure across the two groups (Tables 1 and 2). Overnight polysomnographic findings revealed the anticipated differences in respiratory and sleep measures in those children with OSA when compared to those without OSA, with main differences consisting in reductions in δ sleep in OSA along with increased respiratory events, desaturations, and arousals due to either snoring or following a respiratory event. Although blood pressure measurements did not fulfill any of the criteria for hypertension in the 59 children included in our study, children with OSA had significantly higher mean systolic (113.2 ± 8.3 vs 97.4 ± 7.1 mmHg in children with AHI <1/h TST; $p < 0.05$) and diastolic blood pressures (70.2 ± 5.6 vs 65.7 ± 5.1 mmHg in children with AHI <1/h TST; $p < 0.05$).

3.1. EF testing

3.1.1. One-minute occlusion

To mimic the previous analytic approaches conducted with laser-Doppler flowmetry, we examined the PAT ratio in both the occluded and nonoccluded arm during the initial 30 s after cuff deflation (Fig. 1). As evidenced the postocclusion to preocclusion ratio of the tested arm is divided by the parallel changes of the nonoccluded arm to correct for systemic changes. The example shown is taken from a child with OSA and represents the lack of substantial vasodilation in the postocclusion period. For the group, significantly worse morning than evening PAT reactive hyperemia ratios were apparent among children with moderate to severe OSA (Table 2).

3.1.2. Five-minute occlusion

To mimic the usual procedures conducted in adults, we assessed 27 children. Similar to 1-min occlusion, PAT ratios exhibited progressive and significant deterioration from the evening to morning across categorical OSA severity groups.

For each dataset separately (1 min and 5 min occlusion) and for the whole dataset (59 patients), there was a significant correlation between the deterioration of EF during the night (evening minus morning) and OSA severity. For the whole group, a categorical OSA severity-dependent deterioration in EF was apparent and was particularly prominent in moderate to severe OSA patients (Fig. 2; $p < 0.0007$). There were no significant correlations between only evening or only morning ratios and polysomnographic indices. However, similar to previous studies using laser-Doppler methodologies [11], morning findings differed in children with OSA from controls ($p < 0.03$), while no such differences were apparent in evening tests when analyzed alone.

4. Discussion

The major findings of our study were that PAT reactive hyperemia tests detected significant differences in overnight changes in EF in children with OSA, and that the overnight deteriorations in EF were OSA severity dependent. Thus, alterations in vascular reperfusion kinetics occurred during sleep in children with OSA, and were indicative of compromised integrity of the vasculature that is critical for adequate responses to vasodilatory stimuli such as short ischemic episodes triggered by brachial artery occlusion. Furthermore, there were no differences in the conclusions from our study based on either 1-min or 5-min occlusions, indicating

Table 2
Polysomnographic characteristics of 59 children subdivided based on the occlusion duration used in endothelial function measurements.

	Units	1-Min occlusion time *n* = 32	5-Min occlusion time *n* = 27
TST	(min)	478.1 ± 47.4	378.2 ± 48.3
Sleep efficiency	(%)	86.9 ± 8.2	85.8 ± 6.9
Sleep onset latency	(min)	23.7 ± 23.2	26.3 ± 9.1
REM onset latency	(min)	143.7 ± 59.2	140.2 ± 40.2
Awakenings	(n)	14.3 ± 5.5	14.2 ± 10.0
WASO	(%TST)	4.7 ± 5.1	35.5 ± 21.7
Stage 1	(%TST)	6.1 ± 3.2	5.3 ± 4.3
Stage 2	(%TST)	47.9 ± 7.6	39.3 ± 13.3
Stages 3 and 4	(%TST)	32.2 ± 8.4	36.9 ± 10.8
Stage REM	(%TST)	14.2 ± 6.1	18.6 ± 4.8
SAI	(/h TST)	8.3 ± 6.7	4.9 ± 3.1
AHI	(/h TST)	12.9 ± 8.5	8.5 ± 7.4
O_2 saturation nadir	(%)	86.9 ± 5.8	90.9 ± 4.5
Peak $ETCO_2$	(mmHg)	55.9 ± 2.8	51.0 ± 6.3

Abbreviations: WASO, wake after sleep onset; REM, rapid eye movement; TST, total sleep time; SAI, spontaneous arousal index; AHI, obstructive apnea–hypopnea index; $ETCO_2$, end tidal carbon dioxide.

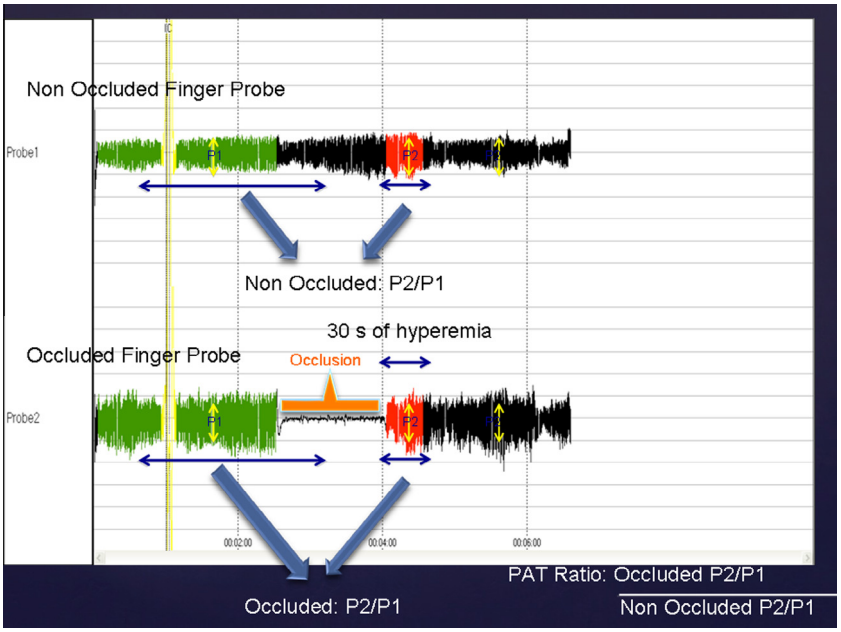

Fig. 1. Illustrative example of a 1-min occlusion-reperfusion test measured with pulse arterial tonometry in a child with OSA with endothelial dysfunction.

that both approaches are valid and can be employed without compromising the validity of the PAT approach.

Before discussing the potential implications of our findings, several methodologic issues deserve comment. First our study confirms and expands on our previous findings of heightened risk for the presence of abnormal EF in children with either obesity or OSA [13]. However, similar to previous studies there was a large degree of variability in vascular function at any level of OSA severity reinforcing the concept that the substantial phenotypic variation in the vasculature may be modulated by a multiplicity of factors, including oxidative and inflammatory processes and elements inherent to genetic susceptibility and environmental conditions [31,32]. Secondly it is highly unlikely that differences in the presence of notable genetic factors for the onset of hypertension or cardiovascular disease may have been the sole contributing factor for the dose-dependent deterioration of EF as assessed by PAT. Thirdly we paid particular attention to exclude any hypertensive children, thereby further minimizing potential confounder effects introduced by elevated arterial blood pressures on the impact of OSA on PAT responses [33]. Lastly our children were evenly distributed across the same age spectrum among the various OSA severity groups, such that discrepancies in age across the groups would not have accounted for the differences in PAT responses that emerged [34,35]. We also should point out that our PAT approach to delineation of ED has been validated against the more widely employed flow-mediated reperfusion tests [17] even though the exact

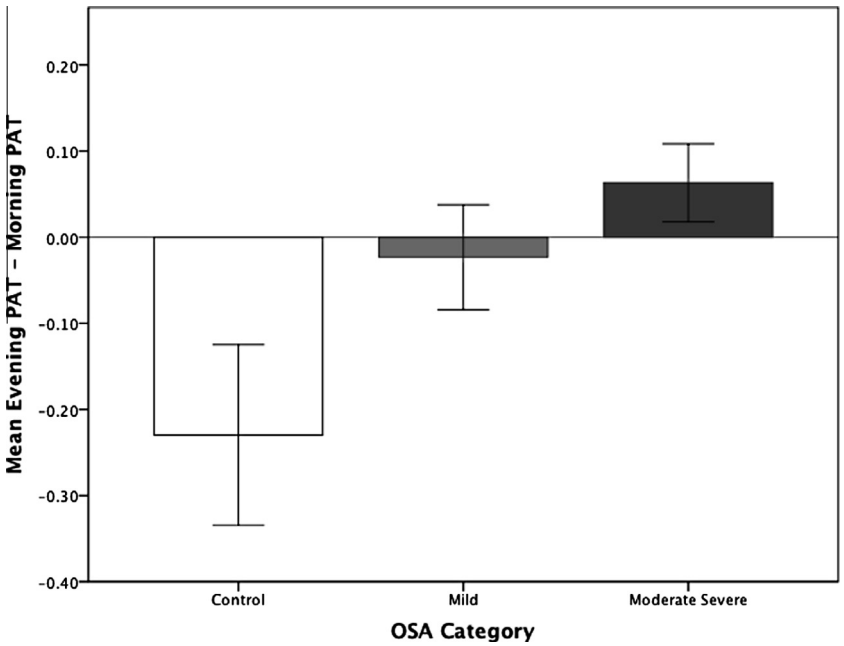

Fig. 2. Peripheral arterial tonometry evening minus morning ratios in 59 children with obstructive sleep apnea of varying severity.

implications of these tests in relation to more classic cardiovascular risk factors, which may not be closely overlapping, may reflect the fact that these discrepancies may underlie different pathologic changes in the vasculature [36].

The mechanisms leading to endothelial injury are only now being actively investigated. The already substantial body of evidence clearly attributes an important role to intermittent hypoxia during sleep, which elicits systemic low-grade inflammatory processes and increased oxidative stress [37–39]. Similar to adults afflicted with OSA, children manifest increased expression of adhesion molecules [40], microparticles [12], and multiple other markers of inflammation [41–44]. Furthermore, nitric oxide (NO) is a major determinant of the vascular postocclusive hyperemic response, such that reduced NO bioavailability must be present [45,46], even if evidence for the presence of endogenous NO synthase inhibitors is lacking [11].

Our study shows for the first time that evening-to-morning differences in EF as measured by PAT are apparent and are particularly worse in children with moderate to severe OSA; therefore, EF possibly reflects the effect of gas exchange alterations, recurrent arousals, and increases in sympathetic activity during the night. As mentioned above, these findings were consistently and independently observed whether or not a 1- or 5-min occlusion time was applied. It will be important in future studies to assess the reversibility of the overnight changes in PAT postocclusive reactivity findings with treatment and also to explore the potential value of PAT in detecting children who are more susceptible to cardiovascular morbidity. Furthermore, it would be of great interest to study if the relatively frequent occurrence of residual sleep-disordered breathing following adenotonsillectomy is indeed associated with similar residual ED and potential future risk for ischemic heart disease. Currently, the most likely hypothesis for the relative absence of OSA-associated cardiovascular disease is the relatively increased recognition of OSA in recent years and application of early treatment. However, the cardiovascular disease risk for the increasingly recognized residual OSA following adenotonsillectomy has not yet been determined.

5. Conclusions

Cardiovascular morbidity has emerged as a relatively frequent complication of pediatric OSA and relatively simple, noninvasive, and well-standardized approaches for detection of EF have been lacking. Our current findings not only reiterate the presence of EF in OSA in otherwise healthy nonhypertensive children but further indicate the potential value of PAT techniques in the investigation of vascular deficits in children with OSA. Furthermore, these changes are apparent as an association between OSA severity and evening-to-morning PAT reperfusion differences, further buttressing the need for detection of otherwise silent end-organ morbidity.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.02.010.

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