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Original Research

SLEEP APNEA

Inflammatory Mediators in Exhaled Breath Condensate of Children With Obstructive Sleep Apnea Syndrome*

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Background: **Upper airway inflammation is now recognized in adults with obstructive sleep apnea (OSA) syndrome. However, the role played by eicosanoids such as leukotrienes and prostaglandins is unclear.**

Objective: **To investigate whether eicosanoids are measurable in exhaled breath condensate (EBC), and to determine whether differences in these inflammatory mediators emerge among children with and without sleep-disordered breathing (SDB).**

Methods: **EBC was collected from 50 consecutive snoring children undergoing overnight polysomnography for suspected SDB, and from 12 nonsnoring control subjects. Prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4), and cysteinyl leukotrienes (cys-LTs: leukotriene C_4 [LTC_4]/leukotriene D_4 [LTD_4]/leukotriene E_4 [LTE_4]) EBC levels were analyzed using enzyme-linked immunosorbent assay.**

Results: **LTB_4 levels were elevated in children with an apnea-hypopnea index (AHI) > 5/h (SDB; 97.6 ± 6.3 pg/mL) compared to children with an AHI < 5/h (mild SDB; 66.4 ± 19.1 pg/mL; $p < 0.01$) and control subjects (27.8 ± 3.7 pg/mL; $p < 0.01$). Similarly, cys-LT (LTC_4/LTD_4/LTE_4) concentrations were also increased in SDB (45.1 ± 10.6 pg/mL in SDB vs 27.6 ± 8.3 pg/mL in mild SDB, and 15.7 ± 7.6 pg/mL in control subjects; $p < 0.01$). In contrast, PGE_2 concentrations were similar among the three groups.**

Conclusions: **Inflammatory mediators such as leukotrienes and prostaglandins can be readily quantified in EBC collected from the upper airway of children. Disease severity-dependent increases in leukotriene concentrations (LTB_4 and LTC_4/LTD_4/LTE_4) emerge among children and may serve as a noninvasive tool in the clinical assessment of these children.** ***(CHEST 2006; 130:143–148)***

Key words: adenoids; eicosanoids; inflammation; leukotrienes; lymphoid hyperplasia; sleep apnea; sleep-disordered breathing; tonsillectomy and adenoidectomy; tonsils

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; cys-LT = cysteinyl leukotriene; EBC = exhaled breath condensate; LTB_4 = leukotriene B_4; LTC_4 = leukotriene C_4; LTD_4 = leukotriene D_4; LTE_4 = leukotriene E_4; OSA = obstructive sleep apnea; PGE_2 = prostaglandin E_2; SDB = sleep-disordered breathing; Spo_2 = oxygen saturation measured using pulse oximetry; T&A = tonsillectomy and adenoidectomy

Obstructive sleep apnea (OSA) syndrome is a common disorder in pediatric patients, affecting 2 to 3% of all children,[1] and is frequently associated with the presence of adenotonsillar hypertrophy.[2,3] If left untreated, OSA can lead to serious morbidity, primarily affecting cognitive, neurobehavioral, and cardiovascular systems.[4–11] Nasal and orophryngeal mucosal inflammation are present in adult patients with OSA,[12–14] and serum C-reactive protein levels, a

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systemic marker for inflammation, are increased in both adults[15] and children with OSA, and correlate with the severity of respiratory disturbance during sleep.[16] More recently, nonsurgical antiinflammatory approaches have been cautiously advocated for sleep-disordered breathing (SDB) in children as an interventional alternative to tonsillectomy and adenoidectomy (T&A). This approach was mainly reserved for those children with SDB not severe enough to justify surgery, or for those with mild residual SDB after T&A, and has shown promising results in open-label, nonrandomized clinical trials.[17–20] We have found that the cloned human cysteinyl leukotriene (cys-LT) receptors 1 and 2[21,22] are highly expressed in the adenoidal and tonsillar tissues of children with SDB.[19,23] Exhaled breath condensate (EBC) can be easily obtained from children[24] and can provide a noninvasive, convenient tool to explore the role of inflammation in the pathogenesis of airway diseases.[25,26] Based on such considerations, we examined the relative abundance of leukotrienes and prostaglandins in the EBC of snoring children with SDB. Our leading hypothesis was that increased levels of inflammation would be present in children with more severe SDB.

Materials and Methods

Patients

The study was approved by the University of Louisville Human Research Committee, and informed consent was obtained from the legal caretaker of each participant. Assent was also obtained from children if they were > 6 years of age. Inclusion criteria were the presence of habitual snoring (snoring as reported by parents > 3 nights per week) and age 6 to 16 years. In addition, 12 children without snoring who underwent overnight polysomnography in the context of another ongoing research study were also included. Exclusion criteria included the presence of craniofacial, neuromuscular, syndromic, or defined genetic abnormalities; current or previous use of montelukast (in the preceding 6 months); acute upper respiratory tract infection; use of any systemic, intranasal, or inhaled corticosteroids or antibiotics in the 4 weeks preceding the initial sleep study; and previous T&A.

Patients were recruited and assessed during their initial clinic visit at Kosair Children's Hospital Sleep Medicine and Apnea Center. The following information was gathered from each participant: age and gender, use of medications (corticosteroids [nasal, inhaled, and systemic], antihistamines, bronchodilators, antibiotics, and leukotriene modifiers) and presence of comorbidity (asthma, allergic rhinitis, and other allergies; attention deficit hyperactivity disorder; psychiatric condition). All subjects were measured (weight and height), and body mass index (BMI) was then calculated (body mass/height^2) and expressed as relative BMI using the following formula: (BMI/BMI of the 50th percentile for age and gender) × 100, based on standardized percentile curves. Children with BMI > 95% were classified as fulfilling the criteria for obesity.

Overnight Polysomnography:

All children participating in the study underwent overnight polysomnography as a part of routine clinical care. Sleep studies were performed in a dedicated, quiet, dark room in the sleep laboratory at Kosair Children's Hospital.

A detailed description and all technical aspects of the polysomnographic recordings are described in detail elsewhere.[19] Analysis of the polysomnogram was performed using standard techniques. In brief, sleep staging was assessed using standard criteria.[27] The obstructive apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time, and obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of at least two breaths. Hypopneas were defined as a decrease in nasal flow of ≥ 50% with a corresponding decrease in oxygen saturation measured using pulse oximetry (Spo_2) ≥ 4% and/or arousal. The mean Spo_2 together with Spo_2 nadir were determined. Arousals were defined as recommended by the American Sleep Disorders Association Task Force report[28] and include respiratory-related (occurring immediately flowing an apnea, hypopnea, or snore), technician-induced, and spontaneous arousals. Arousals were expressed as the total number of arousals per hour of sleep time.

EBC Collection:

EBC was collected from children fitting the inclusion and exclusion criteria and undergoing overnight polysomnography. Nasal expired air was collected over 15 to 20 min using a custom-made collection method modified from Griese et al.[29] For collection, a high-performance, steady negative pressure pump connected to a cold trap (− 5°C) and nasal prongs surrounded on the outer surface by soft foam to allow for improved nasal sealing were used (Fig 1). The children remained sitting throughout the collection period. After cleaning the nose with cold water, a gentle negative suction (3 to 5 mm Hg) was applied to the free end of the tubing at the nasal orifices. The children were asked to breathe normally throughout the collection while they watched television. EBC was collected in cryogenic vials (two vials per patient, each containing approximately 1 mL without addition of any diluent). Samples were immediately taken in ice to a − 80°C freezer for storage. The samples reported herein were collected over a 4-month period and then assayed.

Assays for Inflammatory Markers:

All consecutively collected EBC (from 50 of 56 snoring children and 12 of 12 nonsnoring children) were assayed for

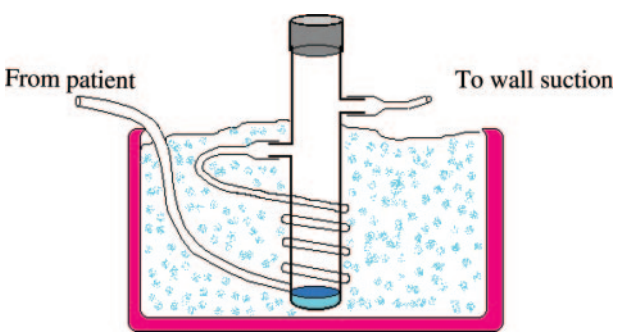

Figure 1. Schematic drawing of the customized method (modified from Griese et al[29]) used to collect EBC from the upper airway in children.

cys-LT levels (leukotriene C_4 [LTC_4]/leukotriene D_4 [LTD_4]/leukotriene E_4 [LTE_4]), leukotriene B_4 (LTB_4), and prostaglandin E_2 (PGE_2) using commercially available enzyme immunoabsorbance kits, as follows: $LTC_4/LTD_4/LTE_4$ (Cayman Chemical; Ann Arbor MI), LTB_4 (Amersham Biosciences; Piscataway NJ), and PGE_2 (Cayman Chemical). Samples were processed in duplicate and assayed in at least two dilutions, and plate reader absorbance results were analyzed with a four-parameter logistic curve fit. The intra-assay and interassay variability for LTB_4, $LTC_4/LTD_4/LTE_4$, and PGE_2 assays were $< 10\%$. The specificity of LTB_4, $LTC_4/LTD_4/LTE_4$, and PGE_2 assays was 100% (except for LTE_4, which was 67%). The detection limits of the assays were 6.2 pg/mL for LTB_4, 7.8 pg/mL for $LTC_4/LTD_4/LTE_4$, and 2 pg/mL for PGE_2. Of note, during the early phases of the project, four sets of samples were run three times over a period of 7 days, 1 month, and 6 months from time of collection, and values for each sample were found to be within $< 10\%$ of each other.

Statistical Analysis:

Results are presented as mean ± SD unless stated otherwise. All analyses were conducted using statistical software (version 11.5; SPPS; Chicago, IL). Comparisons according to group assignment were made with independent *t* tests or analysis of variance followed by *post hoc* comparisons, with p values adjusted for unequal variances when appropriate (Levene test for equality of variances), or χ^2 analyses with Fisher Exact Test (dichotomous outcomes). A two-tailed p value < 0.05 was considered statistically significant.

Results

EBC was collected from 53 of 56 children. Three of the children agreed to participate, but insufficient EBC sample volumes were available. Three remaining children refused to participate. Of the 50 children for whom adequate EBC samples were available, overnight polysomnography revealed that 29 children had an AHI < 5/h of total sleep time (mild SDB) and 21 children had an AHI > 5/h (SDB). For these subgroups, age (9.6 ± 2.9 years vs 10.3 ± 2.7 years) or gender (male gender, 58% vs 57%, respectively) were similar. However BMI was significantly higher in the group with AHI > 5/h (28.6 ± 10.1 kg/m^2 vs 21.6 ± 6.0 kg/m^2; $p = 0.003$). Mean age for the 12 control children was slightly younger (7.1 ± 1.6 years), but both gender (58% male) and BMI (20.8 ± 2.3 kg/m^2) were similar to children with mild SDB. Information regarding comorbidities including asthma, allergic rhinitis, attention deficit hyperactivity disorder, and other psychiatric disorders, as well as the use of medications is presented in Table 1. No differences were observed among the three groups in regard to comorbidities or drug use, except for a slightly increased prevalence of allergic rhinitis among control subjects (Table 1). None of the subjects used corticosteroids or leukotriene modifiers.

Leukotriene enzyme-linked immunosorbent assays revealed higher levels in the SDB group for both LTB_4 and $LTC_4/LTD_4/LTE_4$, compared to children with mild SDB (AHI < 5/h), who in turn had higher levels than control subjects ($p < 0.01$ for all comparisons). Indeed, SDB patients had higher $LTC_4/LTD_4/LTE_4$ concentrations (45.1 ± 10.6 pg/mL) compared to patients with mild SDB (27.6 ± 8.3 pg/mL, $p < 0.01$; Fig 2, *top left*, *A*) and control subjects (15.7 ± 7.6 pg/mL; $p < 0.01$). Similarly, higher LTB_4 concentrations were found in children with SDB in a dose-dependent fashion (97.6 ± 6.3 pg/mL in SDB, vs 66.4 ± 3.6 pg/mL in mild SDB, and 27.8 ± 3.7 pg/mL in control subjects; $p < 0.01$; Fig 2, *top right*, *B*). In contrast, no differences were observed in PGE_2 concentrations among the three groups (Fig 2, *bottom*, *C*).

Table 1—*Characteristics of the Three Groups of Subjects

Characteristics	Control Subjects	Mild SDB	SDB
Age, yr	7.1 ± 1.6	9.6 ± 2.9	10.3 ± 2.7
Male gender	58	58	57
BMI, kg/m^2	20.8 ± 2.3	21.6 ± 6.0	28.6 ± 10.1
Attention deficit hyperactivity disorder (n = 13)	38	31	31
Asthma (n = 7)	28	28	44
Allergic rhinitis (n = 12)	50	16	34
Psychiatric disorder (n = 7)	44	28	28
β_2-Agonists (n = 5)	20	60	20
Antihistamines (n = 3)	33	33	33

*Data are presented as mean ± SD or %.

Discussion

The present study assessed the presence and variance of inflammatory markers in EBC of snoring children undergoing an overnight sleep study for suspected SDB. While PGE_2 levels were similar in patients with mild and moderate-to-severe SDB and in control subjects, EBC leukotriene concentrations were elevated in children with more severe SDB, suggesting the presence of increased inflammation in the upper airway of children in relation to the severity and frequency of upper airway obstructive episodes during sleep. EBC was easily collected in children as young as 6 years of age, suggesting that this noninvasive approach may provide a useful noninvasive method for assessment of upper airway inflammation in the pediatric population. Our experience is compatible with a study[30] in children in which EBC was easily collected from children as young as 4 years of age, and serves as a noninvasive measure of pulmonary inflammation in this young group of patients.[31] We are, however, unaware of

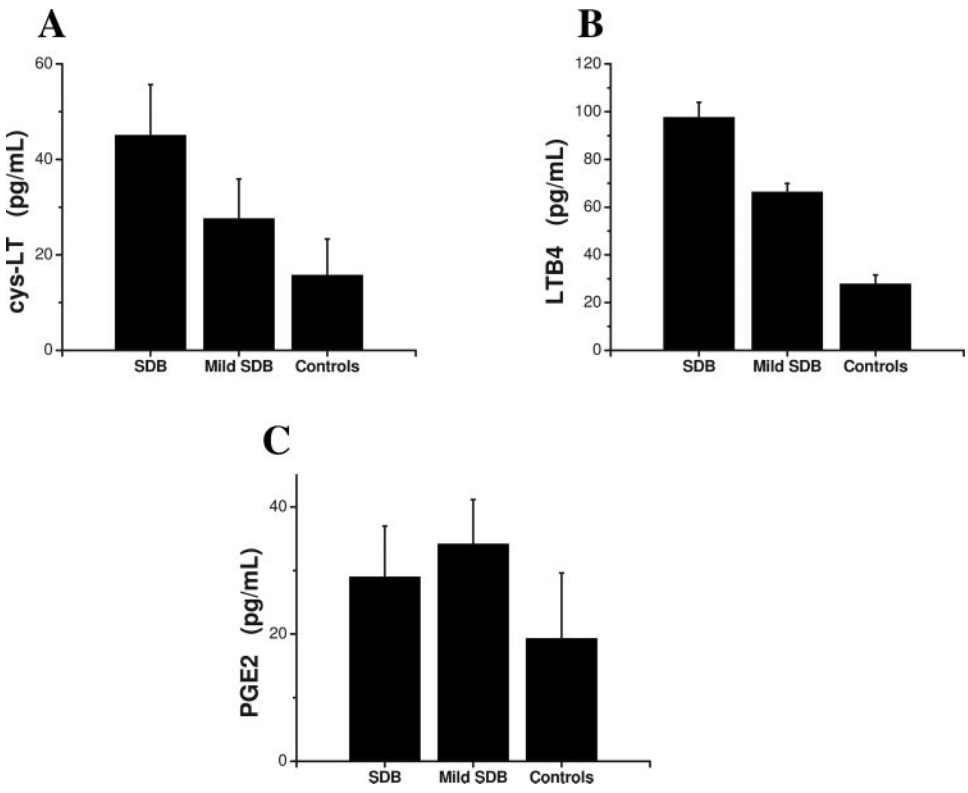

FIGURE 2. *Top left*, *A*: cys-LT (LTC_4/LTD_4/LTE_4) levels in EBC obtained from children with SDB, children with mild SDB, and control subjects (SDB vs mild SDB vs control, $p < 0.01$). *Top right*, *B*: LTB_4 levels in EBC obtained from children with SDB, children with mild SDB, and control subjects (SDB vs mild SDB vs control, $p < 0.01$). *Bottom*, *C*: PGE_2 levels in EBC obtained from children with SDB, children with mild SDB, and control subjects.

leukotriene measurements previously reported in the EBC of adults or children with SDB, such that comparisons between our current findings and those of others is not possible. Nevertheless, a number of investigators have examined the concentrations of leukotrienes in adults with other inflammatory respiratory disorders such as cystic fibrosis,[32] asthma,[33] and COPD during exacerbations, and found such concentrations to be elevated compared to control subjects or during periods of increased disease activity.[34] Increased leukotriene levels have also been reported in EBC of asthmatic children,[35,36] and such levels declined with corticosteroid therapy.[37]

The role of inflammation in the pathogenesis of SDB in children is becoming more established in the last decade. Systemic inflammation, as represented by increased levels of C-reactive protein, was detected in the serum of adults[15] and of children with SDB, and correlated with the degree of disease severity.[16] In addition, regional inflammation of the upper airway has now been described in adults with SDB,[12–14] and such inflammatory changes have been associated with altered innervation of the upper airway mucosa and reduced function of the upper airway dilator musculature in adults with SDB.[38,39] Thus, inflammatory processes appear to be an intrinsic constitutive element of the pathogenesis and dysfunctional properties of the upper airway in SDB.[40]

Of note, a careful analysis of potential confounders among our patients, such as atopy, rhinitis, asthma, and previous history of other allergies suggests that leukotriene concentrations in EBC are increased in pediatric SDB, independent from any of these potential confounders. It is also important to emphasize that it is not possible to exclude a contamination of the EBC from the lower airways using our collection methods, and that therefore we should view the EBC samples as being upper airway enriched, rather than exclusively reflecting upper airway processes.

We previously reported that elevated leukotriene concentrations were present in the adenotonsillar tissues of children with SDB levels undergoing T&A.[19] The current study expands on such findings and shows that elevation of leukotrienes in the upper airway in children with SDB can be identified in snoring children, particularly when their SDB is of sufficient severity as to justify referral for T&A.

Interestingly, unlike other respiratory inflammatory conditions,[41] we did not detect any increases in prostaglandins in the EBC of children with SDB. While we cannot infer the exact pathogenetic mechanisms underlying the activation and enhancement of inflammatory processes within the upper airway of snoring children, and more particularly of those requiring treatment for SDB, the increased expression of leukotrienes may reflect activation of selective subpopulations of inflammatory cells (such as neutrophils or other myeloperoxidase-positive inflammatory cells)[19] that are migrating into these sites of inflammation, or have been up-regulated by the local cytokine milieu within these inflammatory sites (*ie*, tonsils and adenoids). Indeed, neutrophils can migrate into the tonsillar tissues,[42] are known to express cys-LT receptor 1,[19] and therefore could play, similar to other conditions such as asthma,[43] an important role in the proliferation of the lymphadenoid tissue or in the increased upper airway collapsibility associated with SDB in children.[44] While we have previously shown that cys-LT receptor 1 antagonist is of benefit in the management of children with mild SDB,[19] the fact that both LTB_4 and cys-LTs were elevated in the EBC of children with more severe SDB raises the possibility of using a 5-lypooxygenase inhibitor to treat this condition, since this approach would inhibit the synthesis of both LTB_4 and cys-LTs.

Of note, the differences in BMI among the various groups could theoretically influence the degree of inflammation, since obesity has been linked to the increased presence of inflammatory mediators. We believe that upper airway inflammation, manifesting as increased EBC concentrations of leukotrienes, represents local processes within the airway rather than reflect systemic involvement; therefore, the possibility that obesity contributes to this process appears to be less likely.[45]

In summary, we show that EBC can be readily used as a noninvasive correlate of upper airway inflammation in children with SDB. This potentially useful tool may ultimately be of practical assistance in the clinical assessment of snoring pediatric patients.

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