Determinants of Regional Cerebral Oxygenation in Children with Sleep-disordered Breathing

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Rationale: An association between neurocognitive deficits and pediatric sleep-disordered breathing has been suggested; however, weak correlations between disease severity and functional outcomes underscore the lack of knowledge regarding factors modulating cognitive morbidity of sleep-disordered breathing.

Objectives: To identify the parameters affected by sleep-disordered breathing that modulate cerebral oxygenation, an important determinant of cognition. A further objective was to use these parameters with demographic data to develop a predictive statistical model of pediatric cerebral oxygenation.

Methods: Ninety-two children (14 control subjects, 32 with primary snoring, and 46 with obstructive sleep apnea) underwent polysomnography with continuous monitoring of cerebral oxygenation and blood pressure. Analysis of covariance was used to relate the blood pressure, sleep diagnostic parameters, and demographic characteristics to regional cerebral oxygenation.

Measurements and Main Results: To account for anatomic variability, an index of cerebral oxygenation during sleep was derived by referencing the measurement obtained during sleep to that obtained during wakefulness. In a repeated measures model predicting the index of cerebral oxygenation, mean arterial pressure, rapid eye movement (REM) sleep, female sex, age, and oxygen saturation had a positive effect on cerebral oxygenation levels, whereas arousal index and non-REM (NREM) sleep had a negative effect.

Conclusions: Increasing mean arterial pressure, age, oxygen saturation, and REM sleep augment cerebral oxygenation, while sleep-disordered breathing, male sex, arousal index, and NREM sleep diminish it. The proposed model may explain the sources of variability in cognitive function of children with sleep-disordered breathing.

Keywords: children; sleep-disordered breathing; cerebral oxygenation

The pediatric syndrome of sleep-disordered breathing (SDB), which encompasses both primary snoring and obstructive sleep apnea (OSA), affects more than 12% of children (1, 2). Whereas children with primary snoring have only a limited number of obstructive airway events during sleep, those with OSA characteristically experience varying, but more frequent episodes of airway obstruction. Although cognitive deficits have been described in children with SDB, evidence of a causal relationship between SDB and these deficits has not been firmly established (3–9). The absence of a dose-dependent association of cognitive deficits with increasing severity of OSA, coupled with findings of cognitive deficits in children with primary snoring, has challenged the notion of an adverse effect of SDB on cognition (10, 11). To the contrary, however, SDB may indeed be causally related to the

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

An association between neurocognitive deficits and pediatric sleep-disordered breathing has been suggested; however, weak correlations between disease severity and functional outcomes underscore the lack of knowledge regarding factors modulating cognitive morbidity of sleep-disordered breathing.

What This Study Adds to the Field

Increasing mean arterial pressure, age, oxygen saturation, and REM sleep augment cerebral oxygenation, while sleep-disordered breathing, male sex, arousal index, and NREM sleep diminish it. The proposed model may explain the sources of variability in cognitive function of children with sleep-disordered breathing.

development of cognitive deficits, with the biological factors that modify its effect on cognition not yet identified.

There is strong evidence that a sustained decrease of regional cerebral oxygen saturation (rSO_2) during cardiopulmonary bypass surgery in adults is related to postoperative decline in cognitive function (12, 13). Studies have also shown that in adults with OSA, obstructive airway events are associated with transient decreases in rSO_2 (14). Other research has demonstrated an association between OSA and long-term cerebrovascular disease in adults (15).

In view of this combined body of evidence and because of the well-described association between pediatric SDB and cognitive disorders, we hypothesized that pediatric SDB is associated with a dose-dependent, steady-state decrease in rSO_2 during sleep. We tested this hypothesis first by comparing the steady-state difference in rSO_2 between children with SDB and healthy control subjects, and then using these results to develop a predictive, dose-dependent model relating rSO_2 during sleep to its respiratory, cardiovascular, and sleep-related determinants.

METHODS

Subjects

Children ranging in age from 7 to 13 years being treated for nightly snoring and hypertrophy of the tonsils and adenoids were recruited for the study. All of these children underwent overnight polysomnography (PSG) to establish a baseline assessment of breathing during sleep. Children were divided into two subgroups: (1) those with primary snoring (i.e., a PSG showing an apnea–hypopnea index [AHI] of ≤ 1), and (2) those with OSA (i.e., an AHI > 1). Other inclusion criteria were the absence of chronic medical conditions and genetic syndromes. Age- and sex-matched healthy children recruited from our institution and local pediatric practices constituted a control group. Inclusion criteria for this group were the absence of a history of obstructive breathing during sleep

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and the absence of SDB or alveolar hypoventilation on PSG. Children receiving medications for chronic conditions were excluded if they were unable to discontinue these medications during the course of our study. This study was approved by the Cincinnati Children's Hospital Medical Center institutional review board. Parents signed an informed consent before enrollment in the study. Children 7 years of age or older signed an assent form.

Study Design

A medical history was taken, and a physical examination was performed on all children. Next, all underwent standard overnight PSG with simultaneous rSO_2 monitoring (Near Infrared Spectroscopy [NIRS] INVOS 5100 cerebral oximeter; Somanetics, Troy, MI) and beat-to-beat blood pressure measurements (Portapres; TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). PSG studies were performed according to the American Thoracic Society standards (16) using a computerized system (Grass, Telefactor; Astro Inc., West Warwick, RI). Each signal was sampled and stored at 500 Hz.

NIRS

NIRS, a technique for assessing rSO_2 , shows excellent correlation with jugular venous oxygenation (17). Further, the value of monitoring rSO_2 in examining cerebral physiologic functions in normal states and in a number of cardiac and neurologic disorders has been demonstrated in several studies in infants, children, and adults (18–23). Collectively, these studies validate NIRS as a noninvasive method of monitoring rSO_2 in children, and emphasize its clinical applicability across a wide range of ages and disorders.

NIRS measures light absorption by hemoglobin, both in arterioles and capillaries and in the venous system. Because most blood (volumetrically) is held in the venous system, the absorbed light measured is dominated by venous saturation, and thus reflects the balance between oxygen supply and demand in the brain. Hence, NIRS provides information describing tissue metabolism and oxygenation.

NIRS of cerebral blood flow depends on detection of energy emission through the skull and cerebrospinal fluid (CSF). Since skull thickness and amount of CSF vary with individual anatomy, absolute measures of rSO_2 should be normalized. We normalized this measurement using child-specific mean values during wakefulness as the baseline to calculate normalized rSO_2 (ΔrSO_2) values during sleep. As such: $\Delta rSO_2 = rSO_2$ (during sleep) – mean rSO_2 (during wakefulness). Typically, rSO_2 is lower during sleep than during wakefulness.

Data Processing

PSGs were scored for sleep stage and arousals according to accepted standards (24). An obstructive airway event (apnea) was defined as the presence of respiratory effort in the absence or decrease of airflow by more than 80% of the preceding breath and lasting for at least two respiratory cycles. Partial obstructive airway events (hypopnea) were classified as the presence of respiratory effort with a decrease of airflow between 50 and 80% of the preceding respiratory cycle. Central apneas were classified as the cessation of respiratory effort and airflow for at least two respiratory cycles. The AHI was defined as the number of obstructive airway events (apneas, hypopneas, and mixed central and obstructive apneas) per hour of total sleep time. The respiratory arousal index was defined as the total number of respiratory arousals per hour of sleep. All scoring was performed by a single sleep technician and reviewed by the same pediatric sleep physician. After scoring, all signals were indexed according to sleep stage and respiratory event occurrence.

It has been shown in adults that during obstructive events there are parallel changes in systemic oxygen saturation and rSO_2 (14). We anticipated similar changes in children, as systemic oxygen saturation is an important predictor of rSO_2 (25). Our intent in this study was to examine rSO_2 for the whole duration of sleep without the confounding effect of obstructive events. Therefore, data recorded during respiratory events were not used for subsequent analyses.

Statistical Analysis

For each subject, 5-minute signal means were calculated. The means were used in a repeated measures analysis of covariance (ANCOVA) model to determine significant predictors of ΔrSO_2 and to measure difference between groups (control versus primary snoring and control

versus OSA). Diagnostic statistics (predicted residual sums of squares [PRESS]) were calculated to measure any undue individual influences on group mean estimates. Initial covariates in the model included group, age, race, sex, body mass index Z-score (BMIZ), mean arterial blood pressure (MAP), end-tidal CO_2 , oxygen saturation (SO_2), and arousal index. Using fit statistics and residual analysis, a repeated measures model that provided the best fit for each group was identified using a separate auto-regressive moving average covariance structure.

To include stage as a time-varying covariate, 1-minute means of ΔrSO_2 were calculated for each subject. Sleep stage was noted for each 1-minute mean. Where a mean included more than one stage, that mean was not included in the analysis. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were also modeled using 1-minute means in a repeated measures ANCOVA model. Comparisons of least-squares means between control and primary snoring and control and OSA were made using Dunnett's multiple comparison adjustment. Analyses were performed using SAS statistical software (Version 9.1.3; SAS Institute, Cary, NC).

RESULTS

Subjects

Ninety-three children were enrolled in the study. Data from one child in the primary snoring group were identified by the PRESS statistic calculations as exerting an undue influence on the group mean and were eliminated from further analysis (male, age 9, African American, BMI = 22.7, overnight individual mean $\Delta rSO_2 = -15$). Thus, data from 92 children with a mean age of 10.0 ± 1.96 years were included in the analyses. Based on the screening history and PSG results, the study population was subdivided into 32 children with primary snoring, 46 with OSA, and 14 control subjects. All three groups were matched for age, sex, and race. Compared with healthy control subjects, children with primary snoring differed in their BMI, while children with OSA differed in BMI, AHI, and arousal index. The average sleep onset time during which awake baseline rSO_2 was calculated was $50 \text{ min} \pm 31$ minutes. The demographic and PSG data for these groups are shown in Table 1.

TABLE 1. MEANS, STANDARD DEVIATIONS, AND FREQUENCIES FOR DEMOGRAPHIC AND POLYSOMNOGRAPHIC CHARACTERISTICS BY GROUP (CONTROL, PRIMARY SNORING, AND OBSTRUCTIVE SLEEP APNEA)

Variable	Controls (n = 14)	Primary Snoring (n = 32)	OSA (n = 46)	P Value
Male	57%	44%	57%	0.4973
White	57%	56%	57%	0.9984
Age	10.2 (1.9)	10 (1.8)	10 (2)	0.8915
BMI	18 (2.7)	22.3 (6)*	22.3 (5) [†]	0.0261
BMIZ	0.27 (0.9)	1.2 (1)*	1.2 (1) [†]	0.0108
AHI	0.2 (0.3)	0.3 (0.3)	10 (17) [‡]	<0.0001
ETCO ₂ (Sleep)	43 (2)	42 (4)	40 (5) [‡]	0.0394
SaO ₂ (Sleep)	97 (1)	97 (1)	96 (2)	0.1737
% stage 1	4 (2)	4 (4)	4 (2)	0.1916
% stage 2	47 (10)	48 (8)	51 (8)	0.2282
% stage 3	3 (07)	3 (1)	3 (2)	0.9139
% stage 4	28 (8)	28 (6)	26 (7)	0.3052
% REM	18 (4)	16 (5)	16 (5)	0.4354
Arousal index	8 (2)	8 (3)	14 (12) [†]	0.0003
Total sleep time	394 (50)	386 (54)	401 (41)	0.6207

Definition of abbreviations: AHI = apnea hypopnea index; BMI = body mass index; BMIZ = body mass index (Z score); ETCO₂ = end-tidal CO₂; OSA = obstructive sleep apnea; REM = rapid eye movement.

Chi-square tests for association used for sex and race. All other differences tested with Kruskal-Wallis nonparametric test (P values reported for overall test).

* $P = 0.001$, control versus OSA, or control versus primary snoring.

[†] $P < 0.01$, control versus OSA, or control versus primary snoring.

[‡] $P < 0.0001$, control versus OSA, or control versus primary snoring.

Figure 1. Normalized regional cerebral oxygenation (ΔrSO_2) means for sleep stages 1, 2, 3, and 4 and rapid eye movement for control subjects, children with primary snoring, and children with OSA. ΔrSO_2 = difference in cerebral oxygenation between sleep and wake periods; OSA = obstructive sleep apnea.

Determinants of Normalized ΔrSO_2

Modeling ΔrSO_2 without sleep stages. A group comparison of ΔrSO_2 independent of stages of sleep was performed. In a repeated measures analysis that included group, age, race, sex, BMIZ,

MAP, end-tidal CO_2 , SaO_2 , and arousal index as independent variables, the mean ΔrSO_2 significantly differed between children with primary snoring and control subjects ($P = 0.04$; using the Dunnett adjustment for multiple comparisons, $P = 0.07$). There was no difference in ΔrSO_2 between children with OSA and control subjects. The significant predictors (α = parameter estimate for change in intercept; β = parameter estimate for change in slope) of ΔrSO_2 included female sex ($\beta = 0.8$, $P = 0.02$), age ($\beta = 0.2$, $P = 0.005$), MAP ($\beta = 0.06$, $P < 0.0001$), SaO_2 ($\beta = 0.07$, $P = 0.02$), and arousal index ($\beta = -0.04$, $P = 0.02$).

Modeling ΔrSO_2 with sleep stages. ΔrSO_2 characteristically increased from non-rapid eye movement (NREM) to REM sleep for each of the three groups (Figure 1, Table 2). During REM sleep, the rSO_2 levels in children with primary snoring did not reach levels measured during wakefulness. By comparison, the level of rSO_2 exceeded the mean rSO_2 during wakefulness (Figure 1, Table 2) in control subjects and in children with OSA.

As shown in Figure 1, the association between specific sleep stages and ΔrSO_2 differed in control subjects as compared both to children with primary snoring and those with OSA. In control subjects, ΔrSO_2 levels during stage 1 sleep were significantly lower than those during stage 2. There was an opposite association between ΔrSO_2 levels measured in stage 1 and 2 sleep in children with primary snoring and those with OSA. In children with primary snoring, ΔrSO_2 was significantly lower during stages 3 and 4 as compared with stage 2 sleep. In contrast, there was no statistical difference in the ΔrSO_2 levels measured during stage 2 sleep and stages 3 and 4 sleep in control subjects and in children with OSA (Figure 1, Table 2).

In a repeated measures model that included group, stage, group by stage interaction, age, sex, MAP, SaO_2 , and arousal index as independent variables, a significant difference was measured in

Figure 2. Thirty-minute means for (A) ΔrSO_2 , (B) systolic blood pressure, (C) diastolic blood pressure, and (D) mean arterial blood pressure by group. $^{\dagger}P < 0.05$ between control subjects and subjects with OSA; $*P < 0.05$ between control subjects and primary snoring.

TABLE 2. DIFFERENCES IN LEAST SQUARES MEANS FOR ΔrS_{O_2} BETWEEN STAGES 1, 2, 3, AND 4 AND REM SLEEP, WITHIN GROUP (CONTROL, PRIMARY SNORING, AND OBSTRUCTIVE SLEEP APNEA)

Stages	Controls		Primary Snoring		OSA	
	dLSM $\pm$ SE	P Value	dLSM $\pm$ SE	P Value	dLSM $\pm$ SE	P Value
1 versus 2	-0.28 $\pm$ 0.094	0.02	0.37 $\pm$ 0.12	0.01	0.17 $\pm$ 0.07	0.09
1 versus 3-4	-0.41 $\pm$ 0.13	0.01	1.07 $\pm$ 0.17	<0.0001	0.17 $\pm$ 0.10	0.44
1 versus REM	-1.15 $\pm$ 0.13	<0.0001	-0.65 $\pm$ 0.16	0.0005	-0.83 $\pm$ 0.10	<0.0001
2 versus 3 and 4	-0.13 $\pm$ 0.10	1.0	0.70 $\pm$ 0.12	<0.0001	0.01 $\pm$ 0.07	1.0
2 versus REM	-0.87 $\pm$ 0.11	<0.0001	-1.02 $\pm$ 0.13	<0.0001	-1.00 $\pm$ 0.08	<0.0001
3 and 4 versus REM	-0.75 $\pm$ 0.14	<0.0001	-1.72 $\pm$ 0.18	<0.0001	-1.01 $\pm$ 0.10	<0.0001

Definition of abbreviations: ΔrS_{O_2} = change in regional cerebral oxygen saturation; dLSM = Difference $\pm$ SE of ΔrS_{O_2} , least squares means; OSA = obstructive sleep apnea.

P values reflect a Bonferroni multiple-comparison adjustment within group.

ΔrS_{O_2} between children with primary snoring and control subjects ($P = 0.037$; using the Dunnett adjustment for multiple comparisons, $P = 0.06$). After adjustment for multiple comparisons, the differences were significant in stage 2 sleep ($P = 0.04$) and stages 3 and 4 combined ($P = 0.0002$). MAP showed the strongest association with ΔrS_{O_2} (Table 3). Whereas there was a positive association between ΔrS_{O_2} and MAP, age, female sex, and REM sleep, a negative association emerged between ΔrS_{O_2} and NREM sleep and the arousal index. Initial analyses demonstrated that race, BMIZ, and end-tidal CO_2 were not significant predictors of ΔrS_{O_2} , and were excluded from the final model. There was no significant difference in mean ΔrS_{O_2} between children with OSA and control subjects.

SBP, DBP, and MAP during sleep. Blood pressure was significantly higher in children with SDB (Figures 2B, 2C, and 2D). Least squares means analysis of these data show that compared with control subjects, children with primary snoring had higher SBP (89 ± 1 mm Hg versus 95 ± 1 mm Hg; $P = 0.0006$) and MAP (62 ± 0.7 mm Hg versus 65 ± 0.7 mm Hg; $P = 0.002$) than control subjects. Children with OSA differed from control subjects in SBP (99 ± 0.9 mm Hg; $P < 0.0001$), in DBP (52 ± 0.7 mm Hg; $P < 0.0001$), and in MAP (68 ± 0.8 mm Hg; $P < 0.0001$). These differences were measured after controlling for age, sex, race, and BMIZ score (Table 4).

Determinants of ΔrS_{O_2} . The repeated measures model used to determine predictors of ΔrS_{O_2} identified sleep stages, age, sex, Sa_{O_2} , MAP, and arousal index as significant. The direction of the association between ΔrS_{O_2} and age, female sex, and MAP is such that these variables increased, while arousal index decreased rS_{O_2} . Relative to REM sleep, ΔrS_{O_2} decreased during NREM

sleep stages. Based on these findings, a model is proposed in which age, MAP, Sa_{O_2} , and REM sleep diminish the decline in rS_{O_2} during sleep and SDB status, male sex, arousal index, and NREM sleep augment the decline in rS_{O_2} (Figure 3).

DISCUSSION

We have presented data that illustrate the complexity of the association between SDB and rS_{O_2} in children. For example, although increasing arousal indices were associated with decreasing rS_{O_2} , increasing MAP was associated with increasing rS_{O_2} . Nevertheless, both increasing arousal indices and increasing MAP were strongly associated with SDB severity. These data suggest that SDB may have effects that both augment and diminish rS_{O_2} in children. We have proposed a model that has the potential of explaining the variability in end-organ injury and neurocognitive deficits in children with SDB by identifying parameters with competing effects on rS_{O_2} in children.

In the simplest model relating rS_{O_2} to AHI, one would expect to find that rS_{O_2} decreases as AHI increases. As such, we hypothesized that SDB would exert a dose-dependent, steady-state decrease in rS_{O_2} during sleep. Interestingly, however, we found that children with primary snoring had significantly lower ΔrS_{O_2} compared with those with OSA. A likely explanation for these findings is the positive association of ΔrS_{O_2} levels with some of the physiologic parameters affected by SDB. Specifically, we found that ΔrS_{O_2} had a positive association with MAP, Sa_{O_2} , age, and REM sleep. SDB status, increasing arousals, NREM sleep, and male sex had a negative association with ΔrS_{O_2} . The absence of a significant difference in ΔrS_{O_2} between control subjects and children with OSA could thus be attributed to the sum effect of these positive and negative associations in children with OSA.

TABLE 3. PREDICTORS OF ΔrS_{O_2} DERIVED FROM REPEATED MEASURES MODEL USING 1-MIN MEANS WHERE STAGE WAS INCLUDED AS TIME-VARYING COVARIATE

Variable	Estimate	SE	P Value
Group			
Control	-5.0880	1.4343	0.0004
Primary snoring	-5.8452	1.4190	<0.0001
OSA	-5.1093	1.4047	0.0003
Stage 1	-0.6461	0.1646	<0.0001
2	-1.0179	0.1320	<0.0001
3 and 4	-1.7159	0.1768	<0.0001
Female sex	0.8208	0.2902	0.005
Age	0.2502	0.07411	0.0008
MAP	0.05297	0.001701	<0.0001
Sa_{O_2}	-0.00427	0.01188	0.7
Arousal index	-0.05022	0.01673	0.003

Definition of abbreviations: ΔrS_{O_2} = change in regional cerebral oxygen saturation; MAP = mean arterial pressure; OSA = obstructive sleep apnea.

Parameter estimates (SE = standard error) are given.

TABLE 4. PREDICTORS OF SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND MEAN ARTERIAL BLOOD PRESSURE DERIVED FROM REPEATED MEASURES MODEL USING 1-MIN MEANS WHERE STAGE WAS INCLUDED AS TIME-VARYING COVARIATE

Variables	SBP		DBP		MAP	
	F Value	P Value	F Value	P Value	F Value	P Value
Group	22.64	<0.0001	9.52	<0.0001	15.37	<0.0001
Stage	193.89	<0.0001	213.03	<0.0001	226.19	<0.0001
Group by stage	4.86	<0.0001	2.14	0.0461	3.46	0.0020
Sex	0.03	0.8554	3.46	0.0637	1.70	0.1932
Age	24.10	<0.0001	26.75	<0.0001	27.83	<0.0001
Race	5.48	0.0198	0.03	0.8654	1.00	0.3178
BMIZ	1.15	0.2841	6.05	0.0143	3.62	0.0577

Definition of abbreviations: BMIZ = Body mass index Z score; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure.

Figure 3. Schematic of predictive model of regional cerebral oxygenation.

We previously demonstrated that children with OSA have higher 24-hour ambulatory blood pressure compared with healthy control subjects (26). We also demonstrated that elevated ambulatory blood pressure is associated with cardiac remodeling. Collectively, these findings suggest that in the pre-hypertensive stage, elevated blood pressure in children with SDB may contribute to cardiac remodeling, but may also contribute to maintaining normal ΔrSO_2 . Paradoxically, these observations reveal a potential benefit of mild elevation in blood pressure in children with SDB. When evaluating the effect of SDB on neurocognitive function in children, it is thus essential to take blood pressure into account.

Analysis of the influence of demographic characteristics on ΔrSO_2 demonstrated an important sex difference in ΔrSO_2 in response to SDB status. Females were less likely to have a decline in rSO_2 in the presence of SDB. These findings are consistent with many studies that demonstrate a natural sex advantage in cerebral blood flow. At all ages, blood flow to the cerebral hemispheres is greater in females compared with males (27–29). This difference remains statistically significant after adjusting for differences in unit weight of the brain (28). Furthermore, there is evidence of sex differences in the responses of cerebral blood flow to cortical stimulation or oxygen deprivation. In studies of cerebral blood flow using functional magnetic resonance imaging techniques, females demonstrate an enhanced regional cerebral flow in response to visual stimulation (29). Also, in an animal model of incomplete ischemia, females treated with exogenous estradiol maintain a higher cerebral blood flow during ischemia and lower postischemic hyperemia compared with untreated female and male animals (30–32). Taken together, these findings suggest that female sex hormones might have a protective effect against cerebral ischemia reperfusion injury. Thus, it is possible that a higher level of rSO_2 during sleep in females results from a greater baseline cerebral flow. Also, we speculate that female sex hormones may have a protective effect in humans, as seen in animal models (31, 32).

Our analyses identified age as a significant positive predictor of rSO_2 . These results are consistent with those of Kobayashi and coworkers, who showed that regional cerebral blood flow increases with age in childhood (33). Other studies demonstrate that cerebral blood flow is higher in children than in adults (34). These studies corroborate the physical development of the brain, which grows most rapidly during childhood, and reaches a plateau around 12 years old. These results imply that normal cerebral growth could play an important role in modulating the effect of SDB on cerebral oxygenation in children.

There is convincing evidence that rSO_2 levels measured by NIRS are similar to rSO_2 levels measured by cerebral blood flow (21, 35–37), an important determinant of cerebral arterial perfusion pressure. The effect of blood flow on perfusion is influenced to a large extent by systemic blood pressure. Our study further highlighted the role of blood pressure in cerebral oxygenation, demonstrating that MAP exerts a strong positive association with rSO_2 in children during sleep. Although the mechanisms of cerebral oxygenation were not explored, the results suggest that SDB status disturbs the relationship between oxygen supply and demand. Our results point to the likelihood that cerebral metabolic demands are increased in children with SDB.

The study design was based on the objective of measuring differences in rSO_2 during sleep between children with SDB and

matched control subjects. Although we achieved adequate matching on age, sex, and race between groups, more detailed data on pubertal status (Tanner staging [38]) might well have added valuable knowledge about age and sex interactions in modifying rSO_2 during sleep.

Conclusions

The absence of a dose-dependent association of cognitive deficits with increasing severity of OSA may result from the complexity of the relationship between SDB and the parameters that affect rSO_2 . Regional cerebral oxygenation increased in children with increasing MAP, SAO_2 , and during REM sleep. Regional oxygenation is decreased in children with increasing SDB status, arousal index, during NREM sleep. Also, we found that rSO_2 levels increased with age and were higher in females than in males. These physiologic and demographic data are incorporated into a predictive statistical model relating rSO_2 to these parameters in children with SDB. This model may provide an approach to assessing neurocognitive morbidity of SDB in children.

Conflict of Interest Statement: M.A.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. V.S. has served as a consultant to Res Med, Respiration, Cardiac Concepts, Glaxo Smith Kline, and as a speaker at a meeting sponsored by Medtronic and one by Respiration. He is also an investigator on research grants from Sorin, Inc., Respiration Sleep and Breathing Foundation, and ResMed Foundation. M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.Q. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.P.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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