Relationship Between Rem Density, Duty Cycle, and Obstructive Sleep Apnea in Children

Laurie Karamessinis, RPFT; Patricia Galster, RPSGT; Brian Schultz, RPSGT; Joanne Elliott, RPSGT; Thornton A. Mason II, MD, MSCE, PhD; Lee J. Brooks, MD; Paul R. Gallagher, MA; Carole L. Marcus, MBBCh

1The Sleep Center and 2The Division of Biostatistics and Epidemiology, The Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA

Study Objectives: The pattern and distribution of rapid eye movement (REM) sleep changes during development, yet there have been few studies of REM density in children. Although children with obstructive sleep apnea syndrome (OSAS) obstruct primarily during REM sleep, the relationship between REM density and obstructive apnea has not been established for this population. We hypothesized that (i) REM density and REM cycle duration increases over the course of the night in children, (ii) the duty cycle (inspiratory time divided by respiratory cycle time) increases over the course of the night in children with suspected OSAS, and (iii) the increase in REM density over the course of the night is associated with increased severity of obstructive apnea.

Design: REM density and respiratory parameters were measured during polysomnography.

Setting: Sleep laboratory

Patients: 76 children with suspected OSAS.

Interventions: NA

Measurements and Results: REM density and the duration of REM cycles increased over the course of the night until the fifth REM cycle, and then stabilized. The duty cycle increased across the first 6 REM cycles. However, the apnea hypopnea index (AHI) did not increase across REM cycles, and was not affected by the changes in REM density or duty cycle. We speculate that the increase in the duty cycle is a compensatory response to increased upper airway loads during sleep, and that this may lead to ventilatory or upper airway muscle fatigue.

Keywords: Duty cycle, REM cycle, progression of apnea

Citation: Karamessinis L; Galster P; Schultz B et al. Relationship between rem density, duty cycle, and obstructive sleep apnea in children. SLEEP 2007;30(7):837-843.

INTRODUCTION

THE PATTERN AND DISTRIBUTION OF RAPID EYE MOVEMENT (REM) SLEEP CHANGES WITH AGE AND DEVELOPMENT. THE FUNCTION OF REM SLEEP IS UNKNOWN, but it has been speculated that REM sleep is important for memory and learning.1 It is therefore not surprising that infants and young children have more REM sleep than older subjects, and have a different distribution of REM sleep.2 The intensity of tonic REM sleep has been measured using such parameters as the duration of REM sleep and REM latency, whereas the intensity of phasic REM sleep is typically measured by assessing the REM density, i.e., the number of rapid eye movements per unit time.1 Despite the importance of REM sleep in children, there have been few studies evaluating the intensity of REM sleep in the pediatric age group.

Obstructive sleep apnea syndrome (OSAS) is common during childhood, occurring in approximately 2% of young children.9 In children, the overwhelming majority of obstructive events occur during REM.5,6 It has been shown that the severity of obstructive apnea in children is increased in the last third of the night compared to the first third.7 The mechanisms for this are unclear, but it was postulated that this could be due to changes in REM density,5 as phasic REM sleep is associated with central inhibition of ventilation.7,8 Theoretically, muscle hypotonia and central inhibition of breathing may be worse during more intense portions of REM. Alternatively, the worsening of obstructive apnea over the course of the night could be due to increasing upper airway fatigue.7

We therefore hypothesized that: (i) REM density as well as REM cycle duration increases over the course of the night in children; (ii) the duty cycle ( inspiratory time [Tι] divided by total respiratory cycle time [Tr]), or Tι/Tr, a factor that can lead to muscle fatigue9) increases over the course of the night in children with suspected OSAS; and (iii) the increase in REM density over the course of the night is associated with increased severity of obstructive apnea. We therefore measured REM density and cycle duration and respiratory parameters over the course of the night in children with suspected OSAS.

METHODS

Studies were performed in children undergoing polysomnography for suspected OSAS. Routine polysomnography was performed, with the addition of extra electrooculogram leads as described below. REM density, Tι/Tr, and the apnea hypopnea index (AHI) were calculated for each REM cycle, and the change in these parameters over the course of the night was measured.

Study Group

Children with suspected OSAS, aged 2-12 years, were recruited from the Sleep Center at Children’s Hospital of Philadelphia. The younger age limit was chosen to exclude infants and very young...
children, who have more REM than older children. The upper age limit was used to exclude most children in the later stages of puberty, as sex hormones can affect OSAS. The suspicion of OSAS was based on a presenting complaint of habitual snoring associated with additional symptoms, such as labored breathing during sleep or excessive daytime sleepiness. Children with significant, chronic medical conditions other than suspected OSAS secondary to adenotonsillar hypertrophy or obesity were excluded, except for those with mild asthma requiring only intermittent albuterol therapy. Thus, children with genetic syndromes, craniofacial anomalies and neurologic disease were excluded. Children with a history of previous upper airway surgery or previous treatment for OSAS, those on medications known to affect REM sleep, and those with a history of blindness or serious injury to one or both eyes, were also excluded. Subjects were considered obese if their body mass index was greater than the 95th percentile for age, height, and race.

Written informed consent was obtained from the parents/legal guardians. In addition, assent was obtained from children ≥7 years of age. The study was approved by the Institutional Review Board of Children’s Hospital of Philadelphia, and studies were performed according to the Declaration of Helsinki.

Polysomnography

Overnight polysomnography commenced between 20:00-21:00 and ended at 06:00. The following parameters were recorded (using Rembrandt, Medcare, Buffalo, NY): electroencephalogram (C3/A2, C4/A1, O1/A2, O2/A1); submental electromyogram (EMG); tibial EMG; electrocardiogram; chest and abdominal wall motion using standard pediatric criteria, length were scored. Hypopneas were scored if there was a qualitative decrease in oronasal airflow ≥50% associated with paradoxic respiratory efforts, desaturation ≥3%, and/or arousal. The obstructive apnea hypopnea index was defined as the number of obstructive apneas, mixed apneas, and obstructive hypopneas per unit time. Central apneas were also scored, but as very few central apneas occurred, these data are not presented.

Data Analysis

REM was divided into 1-second mini-epochs. The number of eye movements in each mini-epoch and the number of obstructive apneas originating within that epoch were manually calculated, as described in the literature. REM density was defined as the number of eye movements per each 30-second epoch of REM sleep. REM cycles of <2 minutes duration were not included in the analysis. For the purpose of analysis, REM cycles interrupted by <5 minutes of wakefulness or NREM sleep were considered to be part of the same REM cycle. Subjects with fewer than 3 REM cycles during the night were excluded. The obstructive apnea duration was defined as the sum of the duration of all obstructive apneas and hypopneas during each REM cycle. The inspiratory time and total respiratory cycle duration were obtained from the respiratory inductance plethysmographic signal. T1 and T2 were measured for each breath during the first and last minute of each REM cycle.

**Statistical Analysis**

The number of apneas and hypopneas in the first third of the night compared to the last third of the night was compared using the Wilcoxon signed rank test. The difference in REM density (averaged across all REM cycles) between subjects with an AHI <1/hr and those with an AHI >1/hr was performed using the Mann-Whitney rank sum test. The Spearman correlation coefficient was used for correlational analyses. The effect of REM cycle on the various outcomes as measured repeatedly across REM cycles was analyzed based on a longitudinal mixed effects approach. In order to allow for the possibility that change across REM cycles has a curvilinear component, terms for quadratic time and cubic time were included in each model. If these terms were found to be nonsignificant, they were subsequently dropped from the final models. In order to explore the study hypotheses, various models involving time-varying or time-dependent covariates were also examined. For example, the effect of REM density changing across REM cycle on AHI changing across REM cycle was examined by including REM density as a time-dependent covariate and specifying the repeating measures of AHI as the outcome variable. In this study, using several measurements from different REM cycles across the night, the compound symmetry covariance matrix structure was assumed. SAS Proc Mixed models were used.

**RESULTS**

**Study Group**

Seventy-nine subjects were studied. Three subjects were excluded as they had <3 REM cycles during the night. Thus, data were evaluated for 76 subjects. The mean age was 6 ± 3 (SD) years, range 2-12 years. Fifty-six percent were female, and 29% were obese. Polysomnography results are shown in Table 1. Subjects had a wide range of severity of OSAS, as shown in Figure 1. AHI ranged from 0-57/hr, with a median AHI of 1.9/hr.

**REM Architecture**

With the exception of the 3 subjects excluded from the study because they had <3 REM cycles, subjects had 3-8 REM cycles during the night; 5 (7%) subjects had 7 REM cycles, and only 1 (1%) subject had 8 cycles. REM density changed significantly across the REM cycles, with significant linear and quadratic time effects (P = 0.0017 and 0.0245, respectively), indicating a lin-
ear increase and an eventual leveling of REM density by the fifth REM cycle (Figure 2).

There was no correlation between REM density (computed as the mean REM density per subject) and age ($r = 0.11$, $P = 0.37$; Figure 3). In order to compare this study to previous data in the literature, the correlation between REM density and age was reevaluated in those children >6 years of age. There was a slightly stronger relationship, but this still did not reach significance ($r = 0.29$, $P = 0.11$). There was no significant difference in mean REM density between children with an AHI <1/hr and children with an AHI >1/hr ($P = 0.83$).

REM duration changed across the REM cycles, with significant linear and quadratic time effects ($P < 0.0001$ for both linear and quadratic time effects), again indicating a linear increase and an eventual leveling at the fifth cycle (Figure 4).

**Duty Cycle**

$T_i/T_s$ increased significantly across the REM cycles of the night in a linear fashion ($P = 0.0033$). This is shown in Figure 5. Note that very few subjects had more than 6 REM cycles; thus, the apparent decrease in $T_i/T_s$ in cycles 7 and 8 was not significant.

**Apnea Hypopnea Index**

The AHI and obstructive apnea duration variables were severely skewed, with a preponderance of values of zero, and could not be normalized using transformation techniques. Despite the fact that the number of REM obstructive apneas and hypopneas was greater during the last third of the night than the first third (first third, median 0, interquartile range 0–2; last third median 1, interquartile range 0–6.5; $P < 0.001$), there was no significant change in the AHI across the REM cycles of the night ($P = 0.052$ for raw AHI and $P = 0.45$ for log AHI; Figure 6); nor was there a change in total obstructive apnea duration across the REM cycles of the night ($P = 0.13$ for raw values and $P = 0.33$ for log transformed values).

The change in AHI across REM cycles was reevaluated for those subjects who had any degree of airway obstruction, i.e., after excluding those with an AHI = 0. Under these circumstances, log transformation helped to normalize the AHI distribution. There was still no statistically significant change in AHI across the REM cycles of the night in a linear fashion ($P = 0.0033$). This is shown in Figure 5. Note that very few subjects had more than 6 REM cycles; thus, the apparent decrease in $T_i/T_s$ in cycles 7 and 8 was not significant.

**Table 1—Sleep Architecture**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recording time (min)</td>
<td>534 ± 33</td>
<td>466–615</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>459 ± 41</td>
<td>320–530</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>86 ± 9</td>
<td>33–98</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>29 ± 28</td>
<td>2–191</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>37 ± 24</td>
<td>4–121</td>
</tr>
<tr>
<td>Stage 1 (%TST)</td>
<td>7 ± 5</td>
<td>1–27</td>
</tr>
<tr>
<td>Stage 2 (%TST)</td>
<td>46 ± 8</td>
<td>29–66</td>
</tr>
<tr>
<td>Slow wave sleep (%TST)</td>
<td>26 ± 6</td>
<td>10–41</td>
</tr>
<tr>
<td>REM sleep (%TST)</td>
<td>20 ± 5</td>
<td>11–33</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>118 ± 55</td>
<td>35–286</td>
</tr>
<tr>
<td>REM cycles (N)</td>
<td>5 ± 1</td>
<td>3–8</td>
</tr>
<tr>
<td>Arousal index (N/hr)</td>
<td>15 ± 9</td>
<td>5–64</td>
</tr>
<tr>
<td>Apnea hypopnea index (N/hr)</td>
<td>1.9</td>
<td>0–57</td>
</tr>
<tr>
<td>Mean obstructive apnea duration(s)</td>
<td>11.7 ± 3.2</td>
<td>13.2 ± 3.9</td>
</tr>
<tr>
<td>Mean hypopnea duration(s)</td>
<td>88 ± 8</td>
<td>66–98</td>
</tr>
<tr>
<td>Arterial oxygen saturation nadir (%)</td>
<td>51 ± 5</td>
<td>37–64</td>
</tr>
</tbody>
</table>

Data displayed as mean ± SD and range, except for the apnea hypopnea index, which was not normally distributed and is displayed as median and range. TST, total sleep time.

**Figure 1**—The apnea hypopnea index for each of the 76 subjects is shown.

**Figure 2**—The mean (SD) REM density is shown as a function of REM cycles across the course of the night. Note that few subjects had >6 REM cycles.

**Figure 3**—REM density in children, Revision #1 23 Karamessinis

**Figure 4**—REM Cycles

**Figure 5**—The mean (SD) REM density is shown as a function of REM cycles across the course of the night. Note that few subjects had >6 REM cycles.
cycles over the course of the night (P = 0.0751 for raw values; P = 0.12 for log values). Similarly, when only children with moderate OSAS (AHI \( \geq 5 \) hr) were evaluated, there was no statistically significant change in AHI across REM cycles (P = 0.17 for raw values; P = 0.24 for log values). There were 2 subjects who were outliers, with very severe OSAS. One subject with an AHI of 42/hr had 4 REM cycles; her REM AHI for each cycle, respectively, was 131, 120, 77, and 107/hr. The second outlier, with an AHI of 57/hr, had 3 REM cycles, with a REM AHI of 14, 122, and 32/hr, respectively. Thus, neither of the most severely affected subjects had a pattern of worsening during the last REM cycle.

The correlations between AHI and REM density, and AHI and REM duration, were not significant (r = -0.05, P = -0.69; and r = -0.03, P = 0.80; respectively).

**Relationship Between REM Density, Duty Cycle, and AHI**

Although REM density changed across REM cycles, this change in REM density did not have an effect on \( T/I/T_T \) changing across REM cycles. There was no relationship between the changes in either REM density or \( T/I/T_T \) and changes in the AHI across REM cycles.

**Obesity**

There were no significant correlations between body mass index z-scores, which serve as an index of obesity, and AHI (P = 0.19), mean REM density (P = 0.60), or mean \( T/I/T_T \) (P = 0.23) (all parameters computed as the average of the means for each REM cycle).

**DISCUSSION**

This study has shown that REM density and the duration of REM cycles changed over the course of the night in children, with an increase until the fifth REM cycle and then a plateau. The \( T/I/T_T \) increased across REM cycles. However, in contrast to our initial hypothesis, neither the change in REM density nor the change in \( T/I/T_T \) affected the AHI.

**Changes in REM Sleep with Age**

We have shown that both REM duration and REM density increase over the course of the night in preschool-aged children and school-aged children. REM sleep distribution is known to change with age and development. Newborns have a predominance of active sleep, a state analogous to REM sleep, and frequently enter sleep through this stage. The proportion of REM then decreases during childhood, and continues to decrease further during adulthood and old age. Although REM density has been shown to increase over the course of the night in adults, REM density has not been well studied in children. Coble et al evaluated REM density, for the first 4 cycles of the night only, in a somewhat older group of children (6-16 years). They found that REM density tended to increase over the first 4 REM cycles of the night. Our study confirmed this finding in younger children and showed a highly significant increase in REM density across all REM cycles. Coble et al also noted a trend towards...
increased REM density in younger children, although this was only significant for the first and third REM cycles. Hoffman et al.\textsuperscript{24} evaluated REM density in a small sample of females which included 2 prepubertal and 6 pubertal adolescents, and noted increased REM density in the prepubertal compared to the pubertal subjects. We found no relationship between age and REM density when evaluating a younger group of children, although there was a slight trend towards an increased REM density in younger children when only school-aged children were evaluated. Thus, in young children, there is no correlation between REM density and age.

The subjects in the current study had sleep architecture similar to that of a large, somewhat younger, normal population recently reported by Montgomery-Downs et al.,\textsuperscript{25} with a similar total sleep time (459 minutes in the current study compared to 472-475 minutes in the Montgomery-Downs study), a similar percentage of REM sleep (20\% in the current study compared to 20\%-21\% in the Montgomery-Downs study), and a similar number of REM cycles. This is not surprising, as many studies have shown no difference in sleep architecture between children with OSAS and normal controls,\textsuperscript{3} or children with OSAS before and after treatment.\textsuperscript{26,27} The duration of REM cycles across the night increased in the current study, similar to that reported by Montgomery-Downs. However, the Montgomery-Downs study did not evaluate REM density.

Apnea Hypopnea Index

A previous study showed an increase in the REM AHI in the last third of the night compared with the first third of the night.\textsuperscript{3} In that study, the night was arbitrarily divided into thirds, and only the first and last thirds of the night were evaluated, i.e., there was no evaluation of the intervening third. In contrast, the current study used sophisticated analytic techniques to evaluate the entire night. Although the current study found that the number of REM obstructions was greater during the last third of the night compared to the first third, when the intervening REM cycles were taken into account, the AHI did not change significantly across REM cycles. It is most likely that the difference between the 2 studies is due to the different analytic techniques used. Alternatively, the difference may be secondary to the inclusion of subjects with a wide distribution of AHI, as compared with the previous study, which evaluated subjects with more severe disease. However, this is less likely, as the results were similar when only subjects with an AHI $>5$/hr were studied. In addition, neither of the 2 subjects with very severe OSAS had their highest REM AHI during the last REM cycle. The variability in their patterns of AHI illustrates the importance of examining all REM cycles during the night.

Duty Cycle

The duty cycle ($\tau_{REM}/\tau_T$) increased significantly across REM cycles. All of the subjects in this study presented with symptoms of OSAS and a history of habitual nightly snoring. Thus, all of the subjects had varying degrees of increased inspiratory resistance loading during sleep, ranging from snoring alone to obstructive sleep apnea.\textsuperscript{26} A prolonged $\tau_T$ has been shown to occur as a compensatory response to increased inspiratory resistance loading. This response has been shown to occur during both REM and NREM sleep,\textsuperscript{29,30} although the response during sleep is less than during wakefulness. Little is known about the relative contributions of upper airway and ventilatory pump muscles to breathing during sleep in children. In adults during wakefulness, it was recently suggested that the forces generated by these 2 sets of muscles are linearly related,\textsuperscript{11} but this may not apply during sleep. The $\tau_T/\tau_T$ ratio probably represents the combined action of both upper airway muscles and ventilatory pump muscles. It is possible that inspiratory muscle (upper airway and pump) tone decreases as the night progresses, resulting in increased upper airway resistance. This can lead to a compensatory increase in $\tau_T/\tau_T$.

In support of this theory, we have previously shown that normal children have a dramatic decrease in tidal volume in response to inspiratory resistance loading during sleep, accompanied by an increase in $\tau_T/\tau_T$.\textsuperscript{30} In contrast to adults,\textsuperscript{32} children manifest little recovery over time.\textsuperscript{30}

An increased $\tau_T/\tau_T$ may lead to ventilatory muscle fatigue.\textsuperscript{9} This could occur from continued work against an inspiratory load. Although previous studies (in adults) did not find evidence of diaphragmatic fatigue during sleep in patients with OSAS, these studies were all limited to NREM sleep.\textsuperscript{33,34} Furthermore, no studies have evaluated the upper airway muscles for fatigue over time. However, in the current study, the increased $\tau_T/\tau_T$ across REM cycles was not associated with an increase in AHI, even in the more severely affected subjects, suggesting that clinically relevant muscle fatigue did not occur. It is possible that the increase in $\tau_T/\tau_T$ across REM cycles was due to REM-related changes in upper airway neuromotor control or central regulation of ventilation. The latter appears unlikely. Animal studies using the carbachol model for REM sleep have shown a decrease in both inspiratory and expiratory time in response to carbachol injection,\textsuperscript{35} whereas studies in normal adults without sleep disordered breathing showed a decrease in expiratory time and $\tau_T$ in relation to REM density, but little change in $\tau_T$.\textsuperscript{36} These studies are in contrast to the present study, which demonstrated an increase in $\tau_T/\tau_T$.\textsuperscript{30}
Limitations

It should be noted that polysomnograms were terminated at 06:00, due to laboratory scheduling issues. It is likely that some children would have had more REM cycles if they had been allowed to sleep until spontaneous awakening. However, total sleep time, proportion of REM time, and the number of REM cycles were similar to those previously reported for a large cohort of normal children, so it is unlikely that this had a major impact on our results.

Children with OSAS may have a pattern of persistent partial upper airway obstruction associated with hypercapnia, rather than discrete obstructive events. This has been termed obstructive hypoventilation. We did not analyze the relationship between hypercapnia and REM density, as this would have required analyzing the end-tidal PCO$_2$ on a breath-by-breath basis. Future studies of this relationship would be of interest.

Conclusions

In conclusion, we have shown that REM density and the duty cycle ($T_{REM}/T_{TOT}$) increase across REM cycles during the night in children. Despite this, the degree of obstructive apnea does not change significantly across REM cycles.

ACKNOWLEDGMENTS

Dr. Marcus was supported by NIH grants #HL58585, MO1-RR-000240 and U54 RR023567 and research support from Respironics, Inc. that funded a research technician. Dr. Mason was supported by K23 RR16566.

We thank all of the Children’s Hospital of Philadelphia sleep laboratory technologists who helped conduct this study. We are grateful to the children and their families for their enthusiastic participation in this study.

REFERENCES


children, who have more REM than older children. The upper age limit was used to exclude most children in the later stages of puberty, as sex hormones can affect OSAS. The suspicion of OSAS was based on a presenting complaint of habitual snoring associated with additional symptoms, such as labored breathing during sleep or excessive daytime sleepiness. Children with significant, chronic medical conditions other than suspected OSAS secondary to adenotonsillar hypertrophy or obesity were excluded, except for those with mild asthma requiring only intermittent albuterol therapy. Thus, children with genetic syndromes, craniofacial anomalies and neurologic disease were excluded. Children with a history of previous upper airway surgery or previous treatment for OSAS, those on medications known to affect REM sleep, and those with a history of blindness or serious injury to one or both eyes, were also excluded. Subjects were considered obese if their body mass index was greater than the 95th percentile for age, height, and race.

Written informed consent was obtained from the parents/legal guardians. In addition, assent was obtained from children ≥7 years of age. The study was approved by the Institutional Review Board of Children’s Hospital of Philadelphia, and studies were performed according to the Declaration of Helsinki.

Polysomnography

Overnight polysomnography commenced between 20:00-21:00 and ended at 06:00. The following parameters were recorded (using Rembrandt, Medcare, Buffalo, NY): electroencephalogram (C3/A2, C4/A1, O1/A2, O2/A1); submental electromyogram (EMG); tibial EMG; electrocardiogram; chest and abdominal wall motion using standard pediatric criteria, with additional symptoms, such as labored breathing during sleep or excessive daytime sleepiness. Children with significant, chronic medical conditions other than suspected OSAS secondary to adenotonsillar hypertrophy or obesity were excluded, except for those with mild asthma requiring only intermittent albuterol therapy. Thus, children with genetic syndromes, craniofacial anomalies and neurologic disease were excluded. Children with a history of previous upper airway surgery or previous treatment for OSAS, those on medications known to affect REM sleep, and those with a history of blindness or serious injury to one or both eyes, were also excluded. Subjects were considered obese if their body mass index was greater than the 95th percentile for age, height, and race.

Written informed consent was obtained from the parents/legal guardians. In addition, assent was obtained from children ≥7 years of age. The study was approved by the Institutional Review Board of Children’s Hospital of Philadelphia, and studies were performed according to the Declaration of Helsinki.

Statistical Analysis

The number of apneas and hypopneas in the first third of the night compared to the last third of the night was compared using the Wilcoxon signed rank test. The difference in REM density (averaged across all REM cycles) between subjects with an AHI <1/hr and those with an AHI >1/hr was performed using the Mann-Whitney rank sum test. The Spearman correlation coefficient was used for correlational analyses. The effect of REM cycle on the various outcomes as measured repeatedly across REM cycles was analyzed based on a longitudinal mixed effects approach. In order to allow for the possibility that change across REM cycles has a curvilinear component, terms for quadratic time and cubic time were included in each model. If these terms were found to be nonsignificant, they were subsequently dropped from the final models. In order to explore the study hypotheses, various models involving time-varying or time-dependent covariates were also examined. For example, the effect of REM density changing across REM cycle on AHI changing across REM cycle was examined by including REM density as a time-dependent covariate and specifying the repeating measures of AHI as the outcome variable. In this study, using several measurements from different REM cycles across the night, the compound symmetry covariance matrix structure was assumed. SAS Proc Mixed models were used.

RESULTS

Study Group

Seventy-nine subjects were studied. Three subjects were excluded as they had <3 REM cycles during the night. Thus, data were evaluated for 76 subjects. The mean age was 6 ± 3 (SD) years, range 2-12 years. Fifty-six percent were female, and 29% were obese. Polysomnography results are shown in Table 1. Subjects had a wide range of severity of OSAS, as shown in Figure 1. AHI ranged from 0-57/hr, with a median AHI of 1.9/hr.

REM Architecture

With the exception of the 3 subjects excluded from the study because they had <3 REM cycles, subjects had 3-8 REM cycles during the night; 5 (7%) subjects had 7 REM cycles, and only 1 (1%) subject had 8 cycles. REM density changed significantly across the REM cycles, with significant linear and quadratic time effects (P = 0.0017 and 0.0245, respectively), indicating a lin-
ear increase and an eventual leveling of REM density by the fifth REM cycle (Figure 2).

There was no correlation between REM density (computed as the mean REM density per subject) and age (r = 0.11, P = 0.37; Figure 3). In order to compare this study to previous data in the literature, the correlation between REM density and age was reevaluated in those children > 6 years of age. There was a slightly stronger relationship, but this still did not reach significance (r = 0.29, P = 0.11). There was no significant difference in mean REM density between children with an AHI < 1/hr and children with an AHI > 1/hr (P = 0.83).

REM duration changed across the REM cycles, with significant linear and quadratic time effects (P < 0.0001 for both linear and quadratic time effects), again indicating a linear increase and an eventual leveling at the fifth cycle (Figure 4).

**Duty Cycle**

\[ T_{\text{T}} \] increased significantly across the REM cycles of the night in a linear fashion (P = 0.0033). This is shown in Figure 5. Note that very few subjects had more than 6 REM cycles; thus, the apparent decrease in \( T_{\text{T}} \) in cycles 7 and 8 was not significant.

**Apnea Hypopnea Index**

The AHI and obstructive apnea duration variables were severely skewed, with a preponderance of values of zero, and could not be normalized using transformation techniques. Despite the fact that the number of REM obstructive apneas and hypopneas was greater during the last third of the night than the first third (first third, median 0, interquartile range 0–2; last third median 1, interquartile range 0–6.5; P < 0.001), there was no significant change in the AHI across the REM cycles of the night (P = 0.052 for raw AHI and P = 0.45 for log AHI; Figure 6); nor was there a change in total obstructive apnea duration across the REM cycles of the night (P = 0.13 for raw values and P = 0.33 for log transformed values).

The change in AHI across REM cycles was reevaluated for those subjects who had any degree of airway obstruction, i.e., after excluding those with an AHI = 0. Under these circumstances, log transformation helped to normalize the AHI distribution. There was still no statistically significant change in AHI across the REM cycles of the night (P = 0.052 for raw AHI and P = 0.45 for log AHI; Figure 6); nor was there a change in total obstructive apnea duration across the REM cycles of the night (P = 0.13 for raw values and P = 0.33 for log transformed values).
cycles over the course of the night (P = 0.0751 for raw values; P = 0.12 for log values). Similarly, when only children with moderate OSAS (AHI > 5/hr) were evaluated, there was no statistically significant change in AHI across REM cycles (P = 0.17 for raw values; P = 0.24 for log values). There were 2 subjects who were outliers, with very severe OSAS. One subject with an AHI of 42/hr had 4 REM cycles; her REM AHI for each cycle, respectively, was 131, 120, 77, and 107/hr. The second outlier, with an AHI of 57/hr, had 3 REM cycles, with a REM AHI of 14, 122, and 32/hr, respectively. Thus, neither of the most severely affected subjects had a pattern of worsening during the last REM cycle.

The correlations between AHI and REM density, and AHI and REM duration, were not significant (r = -0.05, P = -0.69; and r = -0.03, P = 0.80; respectively).

**Relationship Between REM Density, Duty Cycle, and AHI**

Although REM density changed across REM cycles, this change in REM density did not have an effect on T/TT, changing across REM cycles. There was no relationship between the changes in either REM density or T/TT and changes in the AHI across REM cycles.

**Obesity**

There were no significant correlations between body mass index z-scores, which serve as an index of obesity, and AHI (P = 0.19), mean REM density (P = 0.60), or mean T/TT (P = 0.23) (all parameters computed as the average of the means for each REM cycle).

**DISCUSSION**

This study has shown that REM density and the duration of REM cycles changed over the course of the night in children, with an increase until the fifth REM cycle and then a plateau. The T/TT increased across REM cycles. However, in contrast to our initial hypothesis, neither the change in REM density nor the change in T/TT affected the AHI.

**Changes in REM Sleep with Age**

We have shown that both REM duration and REM density increase over the course of the night in preschool-aged children and school-aged children. REM sleep distribution is known to change with age and development. Newborns have a predominance of active sleep, a state analogous to REM sleep, and frequently enter sleep through this stage. The proportion of REM then decreases during childhood, and continues to decrease further during adulthood and old age. Although REM density has been shown to increase over the course of the night in adults, REM density has not been well studied in children. Coble et al evaluated REM density, for the first 4 cycles of the night only, in a somewhat older group of children (6-16 years). They found that REM density tended to increase over the first 4 REM cycles of the night. Our study confirmed this finding in younger children and showed a highly significant increase in REM density across all REM cycles. Coble et al also noted a trend towards
increased REM density in younger children, although this was only significant for the first and third REM cycles. Hoffman et al.24 evaluated REM density in a small sample of females which included 2 prepubertal and 6 pubertal adolescents, and noted increased REM density in the prepubertal compared to the pubertal subjects. We found no relationship between age and REM density when evaluating a younger group of children, although there was a slight trend towards an increased REM density in younger children when only school-aged children were evaluated. Thus, in young children, there is no correlation between REM density and age.

The subjects in the current study had sleep architecture similar to that of a large, somewhat younger, normal population recently reported by Montgomery-Downs et al.,25 with a similar total sleep time (459 minutes in the current study compared to 472-475 minutes in the Montgomery-Downs study), a similar percentage of REM sleep (20% in the current study compared to 20%-21% in the Montgomery-Downs study), and a similar number of REM cycles. This is not surprising, as many studies have shown no difference in sleep architecture between children with OSAS and normal controls,3 or children with OSAS before and after treatment.26,27 The duration of REM cycles across the night increased in the current study, similar to that reported by Montgomery-Downs. However, the Montgomery-Downs study did not evaluate REM density.

Apnea Hypopnea Index

A previous study showed an increase in the REM AHI in the last third of the night compared with the first third of the night.3 In that study, the night was arbitrarily divided into thirds, and only the first and last thirds of the night were evaluated, i.e., there was no evaluation of the intervening third. In contrast, the current study used sophisticated analytic techniques to evaluate the entire night. Although the current study found that the number of REM obstructions was greater during the last third of the night compared to the first third, when the intervening REM cycles were taken into account, the AHI did not change significantly across REM cycles. It is most likely that the difference between the 2 studies is due to the different analytic techniques used. Alternatively, the difference may be secondary to the inclusion of subjects with a wide distribution of AHI, as compared with the previous study, which evaluated subjects with more severe disease. However, this is less likely, as the results were similar when only subjects with an AHI >5/hr were studied. In addition, neither of the 2 subjects with very severe OSAS had their highest REM AHI during the last REM cycle. The variability in their patterns of AHI illustrates the importance of examining all REM cycles during the night.

Duty Cycle

The duty cycle \((T_f/T_r)\) increased significantly across REM cycles. All of the subjects in this study presented with symptoms of OSAS and a history of habitual nightly snoring. Thus, all of the subjects had varying degrees of increased inspiratory resistance loading during sleep, ranging from snoring alone to obstructive sleep apnea.26 A prolonged \(T_r\) has been shown to occur as a compensatory response to increased inspiratory resistance loading. This response has been shown to occur during both REM and NREM sleep,29,30 although the response during sleep is less than during wakefulness. Little is known about the relative contributions of upper airway and ventilatory pump muscles to breathing during sleep in children. In adults during wakefulness, it was recently suggested that the forces generated by these 2 sets of muscles are linearly related,11 but this may not apply during sleep. The \(T_f/T_r\) ratio probably represents the combined action of both upper airway muscles and ventilatory pump muscles. It is possible that inspiratory muscle (upper airway and pump) tone decreases as the night progresses, resulting in increased upper airway resistance. This can lead to a compensatory increase in \(T_f/T_r\). In support of this theory, we have previously shown that normal children have a dramatic decrease in tidal volume in response to inspiratory resistance loading during sleep, accompanied by an increase in \(T_f/T_r\).30 In contrast to adults,32 children manifest little recovery over time.30

An increased \(T_f/T_r\) may lead to ventilatory muscle fatigue.9 This could occur from continued work against an inspiratory load. Although previous studies (in adults) did not find evidence of diaphragmatic fatigue during sleep in patients with OSAS, these studies were all limited to NREM sleep.33,34 Furthermore, no studies have evaluated the upper airway muscles for fatigue over time. However, in the current study, the increased \(T_f/T_r\) across REM cycles was not associated with an increase in AHI, even in the more severely affected subjects, suggesting that clinically relevant muscle fatigue did not occur. It is possible that the increase in \(T_f/T_r\) across REM cycles was due to REM-related changes in upper airway neuromotor control or central regulation of ventilation. The latter appears unlikely. Animal studies using the carbachol model for REM sleep have shown a decrease in both inspiratory and expiratory time in response to carbachol injection,35 whereas studies in normal adults without sleep disordered breathing showed a decrease in expiratory time and \(T_r\) in relation to REM density, but little change in \(T_f\).36 These studies are in contrast to the present study, which demonstrated an increase in \(T_f/T_{SRT}\).
Limitations

It should be noted that polysomnograms were terminated at 06:00, due to laboratory scheduling issues. It is likely that some children would have had more REM cycles if they had been allowed to sleep until spontaneous awakening. However, total sleep time, proportion of REM time, and the number of REM cycles were similar to those previously reported for a large cohort of normal children, so it is unlikely that this had a major impact on our results.

Children with OSAS may have a pattern of persistent partial upper airway obstruction associated with hypercapnia, rather than discrete obstructive events. This has been termed obstructive hypoventilation. We did not analyze the relationship between hypercapnia and REM density, as this would have required analyzing the end-tidal PCO₂ on a breath-by-breath basis. Future studies of this relationship would be of interest.

Conclusions

In conclusion, we have shown that REM density and the duty cycle (T/Tₜ) increase across REM cycles during the night in children. Despite this, the degree of obstructive apnea does not change significantly across REM cycles.

ACKNOWLEDGMENTS

Dr. Marcus was supported by NIH grants #HL58585, MO1-RR-000240 and U54 RR023567 and research support from Respironics, Inc. that funded a research technician. Dr. Mason was supported by K23 RR16566.

We thank all of the Children’s Hospital of Philadelphia sleep laboratory technologists who helped conduct this study. We are grateful to the children and their families for their enthusiastic participation in this study.

REFERENCES